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# Solid Dispersion: A Comprehensive Review on Formulation Strategies in the Pharmaceutical Industry

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## ABSTRACT

Poor aqueous solubility, especially for the drugs in the Biopharmaceutical Classification System (BCS) Class II, highly permeable and low soluble, is one of the primary drawbacks of the oral pharmaceutical formulation development. Solid dispersion (SD) is a technique under consideration to enhance the dissolution and bioavailability of poorly water-soluble drugs. This general outline covers the principles, types, preparation methods, assessment methods, and mechanisms by which solid dispersions improve the solubility and stability. The solid dispersions are characterized by molecular arrangement (eutectic mixtures, solid solutions, glass suspensions, etc.) or the type of carrier (first to fourth generations). The preparation techniques are hot-melt extrusion, spray drying, and solvent evaporation, yet their advantages and disadvantages are stated. The importance of the polymer selection, polymer-drug complexes, and environmental factors on the physical stability of amorphous systems is another important issue, as illustrated in the paper. The review also describes the effect of solid dispersion on increasing bioavailability by increasing wettability, inhibiting recrystallization, decreasing size, and increasing drug supersaturation. Lastly, the methods used in the characterization of SDs and quality control, e.g., FTIR, DSC, PXRD, and SEM, are also discussed in this review. Despite some weaknesses in scalability and stability, solid dispersion is a powerful and versatile approach for enhancing solubility and enabling effective drug delivery.

## 1. Introduction

The oral route is the most appropriate and favored method of drug administration[1]. Oral delivery tends to promote better patient compliance and treatment adherence compared to other routes. However, for an orally administered drug to be effective, it must dissolve in gastrointestinal (GI) fluids before permeating the GI membrane and entering systemic circulation[2]. poorly water-soluble, limited in their dissolution, and those with low membrane permeability face an absorption barrier due to poor permeation[3].

Scientists enhance the oral bioavailability using the two main methods: (i) increasing the dissolution rate of the poorly water-soluble drugs in addition to their solubility, (ii) enhancing the permeability of the poorly permeable drugs[4] .Several approaches have also been considered to increase the solubility of insoluble drugs in water, including solubilization, cyclodextrin complexation, salt formation , and particle size reduction[5] .Strategies such as physical modifications to enhance surface area , dissolution rate, and the solubility of biocalcification system (BCS) Class II drugs[6–8] (e.g., micronisation, nanoionization, and use of amorphous form or metastable form), while Chemical modifications include pH modification, salt formation, and prodrug development[9] .There is also extensive application of solid dispersion (SD) technologies and surfactant inclusion. In addition, there are new procedures such as supercritical fluid processing, cyclodextrin complexation, and co-solvent systems that are implemented in enhancing the bioavailability of poorly soluble drugs[6,9–15]. The SD formulation has several advantages, including versatility in processing techniques and a wide range of carrier excipients, allowing flexible formulation design for poorly soluble drugs, which is to be administered orally [16].

## 2. Overview

### *2.1Biopharmaceutics Classification System*

The BCS is a scientific model and is used in classifying drug substances based on their intestinal permeability, solubility in aqueous environments, and dissolution rate. NAmidon et al. first suggested the concept of BCS in 1995, before it became one of the most significant tools of pharmaceutical development and regulatory decision-making. It also offers researchers and regulatory authorities the chance to test the behaviour of drug products with the assistance of in vitro information that is useful to a significant extent in the formulation development process and makes bioequivalence testing much easier [17–19].

BCS classifies drugs into [20–22]:

- Class I drugs: These drugs exhibit high solubility and high permeability; hence, they are absorbed easily.
- Class II drugs: These exhibit low solubility but high permeability, meaning dissolution is the rate-limiting step in their absorption.
- Class III drugs: These are drugs that are highly soluble but with low permeability, making membrane transport the limiting factor.
- Class IV drugs: have both low solubility and low permeability, thus constitute most of the problems with formulation and delivery.

Unlike BCS Class II drugs, BCS Class IV drugs exhibit both low solubility and low permeability, making them more challenging for formulation development. Although SD techniques significantly improve solubility, their application for BCS Class IV drugs is limited due to permeability constraints. Therefore, additional strategies such as permeability enhancers or lipid-based systems may be required in combination with SD [23].

These classes are determined based on critical parameters like the solubility of the highest dose in 250 ml of aqueous media across a PH range from 1 to 8, and human

intestinal absorption above 90% for high permeability drugs [24,25]. The dissolution is determined based on USP Apparatus 1 or 2, and a drug is rapidly dissolving if 85% or more of the dose dissolves within 30 minutes in 900 mL of buffer (pH 1.2, pH 4.5, pH 6.8) [26–28].

The advantages of BCS are that it belongs to the group of regulatory tools. It is applied in order to reduce unnecessary human testing, in which case, the

in vitro testing may replace part of the in vivo bioequivalence testing, particularly Class I BCS, and in certain cases, Class III drugs. It not only spares time and money but also provides healthy exposure for the volunteers [22]. BCS can also be used in preclinical research and in the development of formulations, and helps in the decision-making concerning the excipients, the solubilizes, and the delivery systems 29.

Among the four classes, the most interesting one is the BCS Class II drugs. These drugs are highly permeable but poorly soluble. As their in vivo absorption is limited by the dissolution rate, enhancing solubility becomes crucial for improving bioavailability. The Class II compounds, in most cases, could be investigated through in vitro-in vivo relation and additional flexibility of formulation development and regulatory permission [29].

The last discussions have expanded the possibilities of extension of bio waiver to certain drugs in the category of BCS II, specifically, the weak acids, which could have a good solubility in the intestinal pH. This type of drug may be dispensed when it is readily soluble at physiologically effective conditions, and they satisfy permeability criteria [30].

*2.2 Solubility*

In pharmaceuticals, Solubility refers to the ability of a drug to dissolve in bodily fluid, which directly affects its absorption, bioavailability, and therapeutic effectiveness, especially important for poorly water-soluble drugs [31]. Low solubility often results in insufficient dissolution [32]. Solubility is determined by several factors, including temperature, pH, size, and polymorphism of the particle [31,33]. The techniques, such as cosolvency (e.g., ethanol, propylene glycol) [34], hydrotropy (e.g., sodium benzoate) [35], and particle size reduction (micronisation /nanonization) [36], are used to improve solubility. More sophisticated strategies, including SDs 2[0–22,24–27], cyclodextrin complexation [37], and lipid-based preparations 38, enhance solubility, either by alteration of drug structure or by increasing wettability. Technologies used include supercritical fluid recrystallization [32] and spray freezing into liquids (SFL) [32].

*3 Solid dispersions (SDs)*

SDs are defined as "a pharmaceutical formulation technique in which one or more Active Pharmaceutical Ingredients (APIs) are dispersed in an inert carrier or matrix in the solid state [3]. The solid dispersion approach is primarily utilized to (i) improve the solubility of drugs, (ii) enhance their stability, (iii) mask unpleasant or bitter tastes, and (iv) achieve specific drug release profiles [39].

*3.1 Types of SDs*

SDs are classified into two main categories: one based on the carrier used and the second based on the molecular arrangement. Figure 2 shows the types of SDs.

*3.1.1 Types of* SDs *based on the type of carrier used*

SDs are categorised into four generations, each offering distinct advantages in pharmaceutical formulations.

- **First-generation**

Crystalline carriers are employed in the first-generation SDs, e.g., sugars (e.g., dextrose, mannitol). Such systems are thermodynamically stable, are often more crystalline, limiting their dissolution ability in contrast to the amorphous analogues [1,40].

- **Second-generation**

In SDs, the second generation uses amorphous polymers that include polyethene glycol (PEG) and polyvinylpyrrolidone (PVP). They significantly enhance solubility by enhancing drug wettability and preventing recrystallization [41,42].

- **Third generation**

The SDs of the third generation incorporate poloxamer 407 and Gelucire as surfactants that stabilize the amorphous structure of the drug as well as augment its bioavailability, especially in the case of BCS Class II drugs [1,40].

- **Fourth generation**

Fourth-generation SDs offer solubility enhancement and controlled release, involving water-insol-

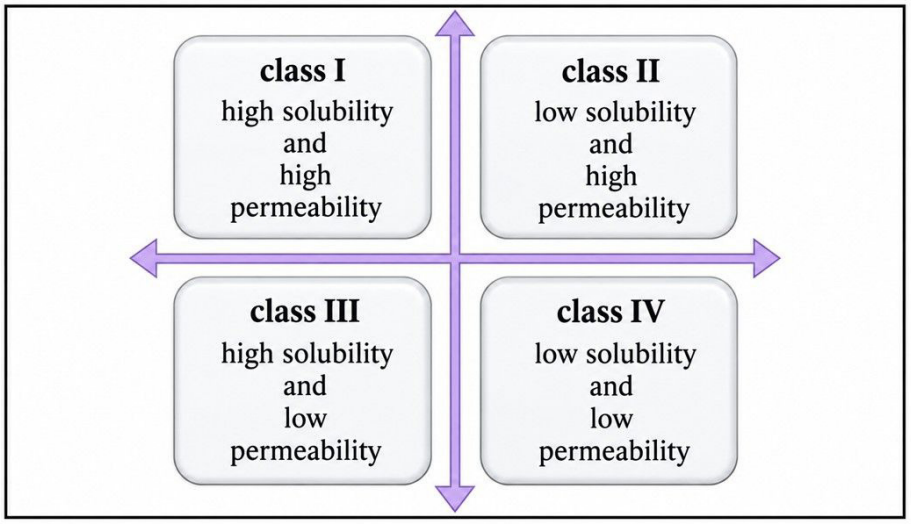


***Figure 1.*** *Biopharmaceutics Classification System (BCS)* [22]

uble carriers like ethyl cellulose. These systems are suitable for drugs requiring a prolonged therapeutic effect.

*3.1.2 Classification of solid dispersion based on its molecular arrangement*

Another way to categorize SDs is based on their molecular arrangement, which has a direct impact on physicochemical behavior and performance.

- **Eutectic mixtures**

When two components crystallize simultaneously from the melt at the eutectic composition, they form a eutectic mixture—a fine, intimately dispersed drug–carrier matrix that significantly improves dissolution rates[3,43,44]. This simultaneous crystallization occurs at the lowest melting point in the binary phase diagram, producing a microstructure in which both drug and carrier exist as crystalline phases separated into domains of solid solutions, often with lamellar or plate-like arrangements[1,44] The dissolution enhancement arises from several factors: ultrafine crystal size of both components at or below the eutectic composition, increased solubility of the drug in the molten carrier, and weakening of the drug's crystal lattice due to the presence of the carrier in the solid solution domains [43,44]. The formation and performance of such eutectic solid dispersions are governed by the drug's crystal energy (melting point and heat of fusion), its lipophilicity (log P), the presence or absence of specific intermolecular interactions with the carrier (e.g., hydrogen bonding), and, when specific interactions occur, the molecular weight of the carrier[43]. Unlike amorphous solid dispersions, eutectic systems are thermodynamically stable while still offering enhanced dissolution, a balance that has been successfully exploited in marketed products such as fenofibrate–polyethylene glycol (Fenoglide®)[44]. Historically, this concept dates back to the 1960s with sulfathiazole–urea and chloramphenicol–urea systems, and it remains a valuable strategy for improving the bioavailability of poorly water-soluble drugs [44].

- **Solid solutions**

One example of dispersion of the drug in the carrier at the molecular level is solid solutions, either in a continuous system of fully miscible components or in a discontinuous system of partially miscible components. These further subdivide into substitutional or interstitial, which allows the drugs to be delivered

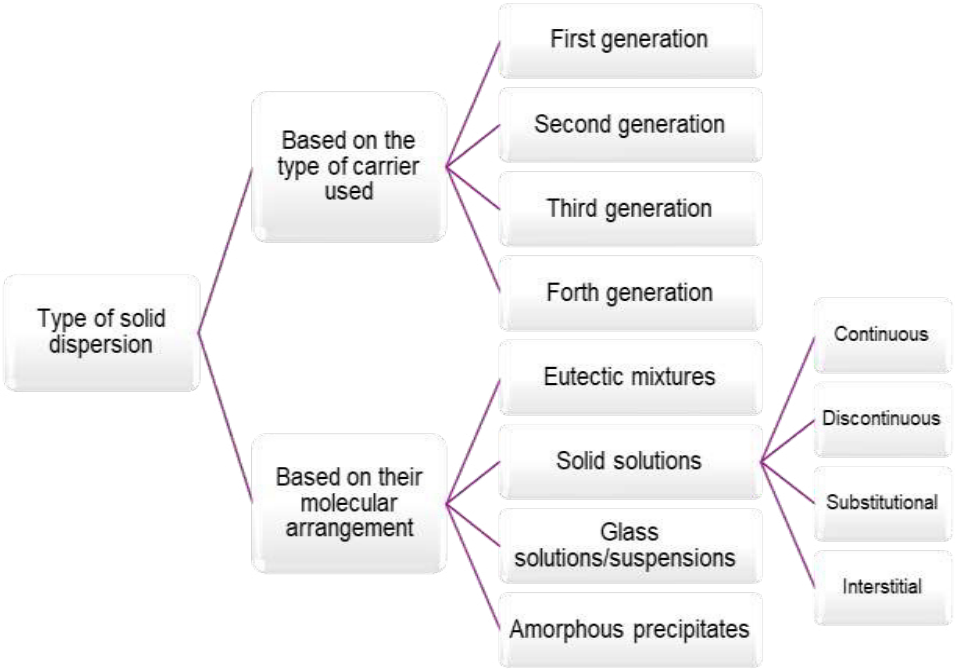


***Figure 2.*** *Type of SDs*[1]

into the body in the most accurate manner [45]. In solid solutions, the drug's particle size is reduced to its absolute minimum molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier itself [46].

– **Continuous Solid Solutions**

In continuous solid solutions, the constituents are completely miscible in all proportions. Theoretically, this implies that the bonding strength between the two components is stronger than the bonding strength within the molecules of each individual component[1]. However, such systems have not yet been reported in the pharmaceutical field [46,47].

– **Discontinuous Solid Solutions**

Discontinuous solid solutions are characterized by a limited solubility of one component in the other 1. For practical purposes, the term "solid solution" is generally applied only when the mutual solubility of the two components exceeds 5%[1]. An example is the sulfathiazole–urea system, where the maximum solid solubility of sulfathiazole in urea is approximately 10% w/w and that of urea in sulfathiazole is about 8% w/w [47]. At the eutectic composition, the system is essentially a physical mixture of these two solid solutions [47].

– **Substitutional Solid Solutions**

This type of solid solution forms when the size difference between the solute and solvent particles is within approximately 15% [1]. In such cases, solute molecules can substitute for solvent molecules in the crystal lattice. The concept originates from metal alloy systems, where substitutional solid solutions occur when the constituent atoms are of similar size and crystal structure [47].

– **Interstitial Solid Solutions**

In interstitial solid solutions, the solute particles occupy the interstitial spaces within the crystal lattice of the solvent. For this to occur, the solute molecules must have a diameter less than 0.59 times that of the solvent molecules [1]. Early hypotheses suggested that drugs could form interstitial solid solutions with crystalline carriers such as polyethylene glycol

**Table1.** Summary of solid dispersion preparation methods.

| Method | Description | Advantages | Limitations | References |
|---|---|---|---|---|
| Kneading | The drug and carrier are mixed into a paste using a minimal solvent, then dried and ground. | Simple, economical, suitable for lab-scale. | Residual solvents, heterogeneity, and limited reproducibility. | 1,6,53 |
| Co-milling | Mechanical blending of drug and carrier without heat or solvent. | Solvent-free, size reduction, and potential amorphization. | Low physical stability, weak drug-polymer interaction. | 1,6,54 |
| Fusion (Melting) | Drug and carrier melted together, rapidly cooled, and pulverized. | Solvent-free, cost-effective. | Not suitable for thermolabile drugs, risk of phase separation. | 48 |
| Microwave Fusion | Fusion is aided by microwave radiation for rapid heating. | Quick, uniform heating, energy efficient. | Difficult to scale up. | 55,57 |
| Hot-Melt Extrusion | A drug-polymer mix is processed in an extruder through multiple heated zones and then extruded. | Continuous, scalable, good mixing. | Requires high temp, high shear, not suitable for heat-sensitive drugs. | 4,58 |
| KinetiSol® | High-shear, heat-free fusion using rotating blades to generate frictional heat. | Ideal for thermolabile drugs, high throughput (up to 1000 kg/h). | Specialized equipment required. | 55,60 |
| Solvent Evaporation | The drug and carrier are dissolved in the solvent, then evaporated under reduced pressure. | Good for heat-sensitive drugs. | Solvent toxicity, risk of phase separation. | 53 |
| Spray Drying | The atomized solution is dried in hot air to produce fine particles. | Scalable, fast drying, and control over particle size. | Requires drug-carrier solubility in volatile solvents. | 62,63 |
| Lyophilization | Freeze-drying of drug-polymer solution by | Excellent for thermally sensitive drugs, with | Expensive, time-consuming. | 64 |

| | | | | |
|---|---|---|---|---|
| | sublimation under vacuum. | high homogeneity. | | |
| Electrospinning | High-voltage field creates drug-loaded nanofibers from polymer solution. | High surface area, improved dissolution. | Poor scalability, experimental stage. | 65,66 |
| Fluid-Bed Coating | Solution sprayed on fluidized particles to form coated granules. | Suitable for tablets/capsules, scalable. | The process is tedious and time-consuming. | 67 |
| Supercritical Fluid | Supercritical $CO_2$ is used to precipitate drug-carrier dispersion. | Solvent-free, good flow, and particle properties. | Requires high-cost equipment and complex control. | 68 |
| Solvent-Melt | Drug dissolved in solvent, then added to molten carrier; solvent removed. | Combining fusion and evaporation benefits. | Possible solvent residues, thermal limitations. | 41,71 |
| Co-precipitation | The drug and carrier are dissolved in different solvents, mixed, and precipitated. | Allows the use of less volatile solvents and solvent reuse. | Solvent incompatibility, drying issues. | 69,70 |

(PEG) [47]. However, subsequent research revealed that molecularly dispersed drugs in such systems predominantly reside in the amorphous regions of the carrier rather than in true interstitial crystalline sites [47].

- **Glass solutions and suspensions**

Glass solutions and suspensions represent a class of solid dispersions in which the drug is dispersed within an amorphous carrier. A glass solution is a homogeneous, glassy system in which the drug is molecularly dispersed, whereas a glass suspension consists of precipitated amorphous drug particles suspended in a glassy carrier [48]. The glassy state is characterized by transparency, brittleness, and the absence of a sharp melting point; instead, materials soften progressively upon heating [48]. Common carriers that favor the formation of glass solutions include amorphous polymers such as PVP, poly-vinyl-pyrro-lidone-co-vinyl-acetate (PVPVA), hydroxy propyl methyl cellulose (HPMC), as well as various sugars like sucrose, trehalose, and inulin [47]. This class currently represents the most intensively studied and applied solid dispersion system [47]. Although glass solutions enhance solubility by reducing the drug to a molecular state requiring no energy to break the crystal lattice upon dissolution they are thermodynamically unstable and may require stabilizers to prevent recrystallization [48]. Upon contact with gastrointestinal fluids, the hydrophilic carrier dissolves, releasing the drug into a supersaturated solution;

**Table 2.** Summary of materials used in solid dispersions and summary of previous reports

| Carrier Class | Specific Carriers | Key Properties | Drug (BCS Class) | Preparation Method | Key Outcome | Reference(s) |
|---|---|---|---|---|---|---|
| **Vinyl Pyrrolidone Derivatives** | PVP K30, Copovidone (PVPVA) | Amorphous, high Tg (163 °C for PVP K30; 100 °C for Copovidone), hydrophilic, good hydrogen-bond donor/acceptor, soluble in organic solvents | Telaprevir (II) | Co-milling | Solid dispersion stabilized by hydrogen bonds; improved solubility and cytotoxicity profile | 1,41,51,72 |
| | Copovidone (PVPVA) | | Lopinavir/ Ritonavir (II/II) | Hot-melt extrusion | Kaletra®; first marketed fixed-dose combination using solid dispersion; enhanced oral bioavailability | 51,72 |
| | PVP K30 | | Curcumin (IV) | Solvent evaporation | Enhanced solubility, anti-inflammatory activity; stabilized via intermolecular hydrogen bonding | 1,41 |
| **Polyethylene Glycols (PEG)** | PEG 4000, 6000, 8000 | Crystalline (semi-crystalline), low melting range (55–63 °C), water-soluble, waxy, limited solid solubility for drugs | Fenofibrate (II) | Fusion (melt) | Eutectic solid dispersion with 25% drug loading; improved dissolution compared to pure drug; lamellar microstructure | 43,51,72 |
| | PEG 6000 | | Griseofulvin (II) | Fusion | Gris-PEG®; first marketed solid dispersion; enhanced dissolution and absorption | 1,41 |
| | PEG 6000 | | Celecoxib (II) | Spray drying | 100% dissolution in 1 h (vs. 59% for pure drug); improved oral absorption | 1 |
| **Cellulose Derivatives** | HPMC (e.g., HPMC-E, K) | Amorphous, high Tg (141–172 °C), hydrophilic, forms gel layer, excellent crystallization inhibition | Itraconazole (II) | Spray layering | Sporanox®; supersaturation maintained in intestine; marketed product | 1,72 |
| | HPMCAS (L, M, H) | Amorphous, amphiphilic, enteric (pKa ≈ 5), Tg ≈ 120 °C, forms nano-colloidal phases in intestinal pH | Telaprevir (II) | Spray drying | Incivek®; amorphous solid dispersion with enhanced bioavailability; marketed | 72 |
| | HPMCAS | | Nimodipine (II) | Spray drying | High-loading crystalline solid dispersion (90%) with 60% cumulative dissolution; stable for 3 months at 40 °C/75% RH | 49] |
| | HPC-SL | | Nimodipine (II) | Wet milling and spray drying | High drug loading (90%) crystalline solid dispersion; improved dissolution and stability | 49 |
| **Amphiphilic Polymers** | Soluplus® (PVCL-PVA-PEG) | Amorphous, low Tg (70 °C), forms micelles, good solubility in organic solvents and water | Andrographolide (II) | Hot-melt extrusion | Improved dissolution via hydrogen bonding and micellization; enhanced absorption | 72 |
| | Soluplus® | | Itraconazole (II) | Hot-melt extrusion | Sustained supersaturation; drug-polymer hydrogen bonding prevented recrystallization | 50 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Surfactants (used with polymers)** | TPGS | Crystalline, surfactant, CMC 0.02 mg/mL, solubilizer, P-gp inhibitor | Itraconazole (II) | Hot-melt extrusion (HPMCAS/TPGS) | 1.8-fold increase in AUC vs. Sporanox®; synergistic precipitation inhibition (thermodynamic + kinetic) | 50 |
| | SDS, Poloxamer 188 | Anionic/non-ionic surfactants | Various BCS II drugs | Combined with HPMCAS or PVP | Increased solubility and wetting; stabilization of nanosuspensions during milling | 49,72 |

however, such metastable solutions are prone to precipitation unless kinetically stabilized [47]. To achieve physical stability, carriers with high glass transition temperatures (Tg) are preferred, as molecular mobility becomes negligible approximately 50 °C below Tg, thereby inhibiting phase separation and crystallization [47]. Additionally, the formation of hydrogen bonds between the drug and carrier plays a crucial role in stabilization by preventing drug–drug interactions and increasing the activation energy for crystallization [47]. Many glass solutions are inherently supersaturated in the solid state, meaning their stability relies heavily on kinetic stabilization (antiplasticization) rather than thermodynamic equilibrium [47]. Thus, carrier selection based on high Tg, hydrogen-bonding capacity, and miscibility with the drug is essential for developing robust glass solution formulations [47,48].

- **Amorphous precipitates**

Amorphous precipitates in crystalline carriers, such as polyethene glycol (PEG), utilize the drug's amorphous nature to promote rapid dissolution [1]. This amorphous state is a high-energy form that lacks long-range molecular order, which significantly enhances the apparent solubility and dissolution rate of poorly water-soluble drugs compared to their crystalline counterparts [47]. However, the amorphous state is thermodynamically unstable and possesses excess free energy, making it prone to recrystallization during storage, which can lead to a loss of dissolution advantage [47,49]. When the drug loading exceeds the miscibility or solid solubility of the drug in the crystalline carrier, the system becomes supersaturated in the solid state, increasing the risk of amorphous phase separation followed by crystallization [49]. To mitigate this instability, formulation strategies often incorporate stabilizers such as polymers or surfactants that inhibit nucleation and crystal growth by increasing viscosity, providing steric hindrance, or forming hydrogen bonds with the drug [47,50]. For example, the addition of hydroxypropyl methylcellulose acetate succinate (HPMC AS) with surfactants like D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) in amorphous solid dispersions can synergistically delay drug precipitation by reducing the degree of supersaturation and adsorbing onto crystal surfaces, thereby maintaining the drug in a supersaturated solution for enhanced absorption[50]. Thus, while amorphous precipitates in crystalline carriers offer rapid dissolution benefits, careful selection of carriers and stabilizers is essential to ensure physical stability and consistent performance.

*3.3 Preparation of SDs*

- **Kneading Method**

The kneading process entails the triturating of the drug with a hydrophilic carrier in a small quantity of solvent, usually water, ethanol, or acetone, up to the point of attaining a paste. This paste is then dried and afterwards vacuum dried and reduced into small particles [51,52]. It is believed to be a simple and economical technique. The disadvantages of individuals, in turn, are heterogeneity and residual solvents, which can affect the physicochemical stability of the product [41,53].

- **Co-Milling Method**

This method involves physical mixing of the carrier and the drug without using heating or solvents, which is called mechanical activation or co-milling. Through the milling of the mixture, the whole procedure is subjected to a long duration of time, mostly

at ambient or regulated temperatures. The method decreases the particle size and is able to transform crystalline drugs into amorphous forms. Nevertheless, it can cause low homogeneity and physical stability because of the ineffective interactions between drugs and polymer [53,54].

- **Fusion or Melting Method**

This method, first suggested by Sekiguchi and Obi in 1961, involves melting a physical mixture of polymer and drug, followed by rapid cooling and solidification. The final mass is then crushed and sieved to yield a fine powder [48].

Modifications of the fusion method:

**Microwave-assisted fusion**: Offers rapid and uniform heating. It is energy-efficient but may present challenges in scale-up [55–57].

**Hot-Melt Extrusion (HME)**: It involves intense mixing at high temperatures and shear forces, suitable for continuous processing. It is widely used for scalable manufacturing of SDs [4,58,59].

**KinetiSol® Dispersing**: A high-shear fusion technique without external heating. This method generates heat through mechanical friction and is ideal for thermolabile drugs. It offers high throughput (up to 1000 kg/h), making it suitable for commercial manufacturing [55,60].

- **Solvent Evaporation Methods**

These involve dissolving the drug and carrier in a common solvent, followed by solvent removal. The methods include:

**Simple Solvent Evaporation**: After forming a homogeneous solution, the solvent is evaporated under reduced pressure or ambient conditions. It is suitable for thermolabile compounds but carries the risk of residual solvent and phase separation [61].

– **Spray Drying**: Here, the drug-carrier solution is sprayed into a hot drying chamber. Producing fine, amorphous powders with improved flow properties [62,63].

**Lyophilisation (Freeze Drying)**: Involves freezing the drug-carrier solution, followed by sublimation of the solvent. It ensures homogeneity and is suitable for heat-sensitive compounds, though it is cost-intensive [64].

**Electrospinning**: This method uses a high voltage on the polymer-drug solution, which produces ultrafine fibers. This high surface area enhances dissolution [65,66].

**Fluid-Bed Coating**: Drug solutions are sprayed onto inert cores or granules under fluidized conditions. This method is useful for tablet and capsule preparation [67].

- **Supercritical Fluid (SCF) Technology**

This technique uses supercritical $CO_2$ as a solvent or ant solvent to produce SDs. SCF technology is solvent-free and results in better powder flow and dissolution enhancement. However, specialized equipment and process optimization are needed for scale-up [68].

- **Co-Precipitation Method**

Also referred to as co-evaporation, it involves dissolving the drug and polymer in different solvents (e.g., aqueous and organic), followed by mixing and solvent removal. It ensures molecular dispersion and enhanced solubility [69,70].

- **Melting-Solvent (Melt Evaporation) Method**

A hybrid of fusion and solvent evaporation, this technique includes dissolving the drug in a solvent and adding it to the molten carrier, followed by solvent removal. It combines the advantages of both methods, making it suitable for thermostable drugs [41,71]. Table 1. Shows a summary of SD preparation methods.

*3.4 Materials Used for SDs*

Materials used for SDS are presented in Table 2.

*3.5 Evaluation of SDs*

- **Dissolution study**

Studies of dissolution are particularly crucial in assessing the improvement of solubility and bioavailability of poorly soluble drugs. The most studied practice is the application of SD with hydrophilic carriers, which has the capability of increasing drug dissolution rate by many folds over its pure state or physical mixtures. To verify the dissolution character of SD, scientists prepare samples by mixing drugs

**Table3.** Advantages and disadvantages of solid dispersion

| Aspect | Advantages | Disadvantages | References |
|---|---|---|---|
| Solubility | Boosts solubility of poorly soluble drugs via amorphous state, enabling supersaturation. Ideal for BCS Class II drugs. | Reduced solubility due to water-induced crystallization and phase separation. | 45,111–113 |
| Dissolution Rate | Enhances dissolution via high-energy amorphous state, smaller particles, and increased wettability/porosity. | Crystallization in aqueous media slows dissolution. Viscous polymers may hinder release. | 45,111–116 |
| Bioavailability | Improves bioavailability through better solubility/dissolution, aiding GI absorption and compliance. | Polymers/water lower drug potential, reducing bioavailability. Limited commercial use due to instability. | 45,111–115 |
| Physical Stability | Polymers (e.g., PVP, HPMC) raise Tg, inhibit crystallization, and enhance stability. | Prone to crystallization in humid conditions as water lowers Tg, causing instability. | 45,112–116 |
| Formulation Flexibility | Diverse carriers tailor release profiles; sugars mask taste; suitable for fast-disintegrating tablets. | A complex drug-polymer-water system hinders predictability. Dosage form integration and reproducibility are challenging. Some carriers are hygroscopic/toxic. | 113–116 |
| Thermodynamic Predictability | Flory-Huggins/Gibbs-Duhem models predict solubility via amorphization and mixing. | Inaccurate interaction parameter ($\chi$) estimates cause prediction errors. | 117 |
| Experimental Reliability | Intrinsic dissolution testing ensures accurate solubility measures. | Solubility deviates due to solute changes and crystallization. Expensive, heterogeneous production limits scalability. | 112,114,117 |

with polymers and see how the drug is released when placed in a solvent under controlled conditions. One such method widely used is a UV–Vis fiber optic probe system, which monitors drug concentration in real-time by finding out how much light the solution absorbs at certain wavelengths. This helps in keeping track of the amount of drug that dissolves, and procedures like second-derivative UV analysis are used to limit the interference of the undissolved particles. Additional apparatus, such as Dynamic Light Scattering, is generally employed for the determination of particle size and growth of small particles (nanoparticles), which may be developed in dissolution, particularly if polymer concentration is high. In addition to determining the quantity of drug still dissolved, $^{1}$H Nuclear Magnetic Resonance (NMR) spectroscopy is used. Cross-polarised light microscopy is also used to visually establish if the drug particles are disintegrating or beginning to recrystallise throughout the test [73,74].

Another technique that is regularly employed uses the USP Type II (rotating paddle or disk) dissolution apparatus, where drug-polymer blends are immersed in an aqueous environment under controlled pH, stirring, and temperature to determine the rate and extent of drug release. Scientists can vary the rate of stirring, temperature, or acidity to record the impact of such factors on the release rate. In other research, mathematical models are constructed to explain the process. For instance, a chemical-potential-gradient model can be utilized in explaining two-step drug release: step one involves drug diffusing from the solid surface into the liquid, and step two involves it diffusing through the residual solution. The model can be combined with thermodynamic equations (e.g., PC-SAFT) to predict how the drug will perform in different formulations and conditions, so scientists can know whether the process is controlled by release from the surface or diffusion from within the liquid [75].

**Acceptance criteria:** For immediate-release solid dispersions, ≥80% (or 85%) should dissolve within 30–60 min. Batch similarity is confirmed with $f_2 \geq 50 f_2 \geq 50$. Multipoint specifications apply for modified release. The method must discriminate changes in crystallinity or polymer composition [76,77].

- **Content uniformity**

To ensure that every tablet or capsule in a batch has the same quantity of API, content uniformity testing is conducted. This is achieved by blending the drug with other drugs (excipients) to form a consistent blend. To achieve a quality blend, crucial parameters such as how long the powder is blended, the rate of blending, and the weight of the blender powder need to be stringently controlled, depending on the form of the material and the equipment being used. With improper mixing—either too much or too little—it can result in uneven drug distribution. That is why in-process inspection or sampling is typically done during blending to determine that the blend is homogeneous before proceeding [78].

The official method for content uniformity testing involves analyzing individual dosage units (in USP <905>, typically 10), typically using high-performance liquid chromatography (HPLC). Although HPLC provides high accuracy and sensitivity, it is time-consuming and requires extensive sample preparation. Alternative methods such as UV–Vis spectroscopy are also used; however, they share similar limitations and may not be suitable for all formulations [78].

To solve such issues, new tools such as near-infrared (NIR) and Raman spectroscopy are increasingly employed today. They are quick, non-destructive, and can be used in the mixing process itself or even on tablets. NIR is based on the use of sensors that are placed directly inside the blender to track the consistency of drug mixing without sampling out. Raman spectroscopy, especially Transmission Raman Spectroscopy, is able to measure how much drug is present in a full tablet quickly and accurately by analysing a high percentage of the sample, as opposed to the surface [78].

Finally, it is of critical importance to utilise the proper sampling process in order to ensure results are representative of the entire batch. Standard methods include random sampling, stratified sampling (from various areas within the batch), and systematic sampling (sampling at regular intervals in manufacturing). New guidance, such as USP <1905>,

is currently being written to enhance sampling practice so that it better represents the actual quality of the entire batch and keeps pace with regulatory requirements [78].

**Acceptance criteria:** Per USP <905>, the acceptance value (AV) must be ≤15.0. Stage 1: 10 units; if AV ≤15.0, batch passes. Stage 2: 30 units total, AV ≤15.0 and no individual unit outside 75–125%. Many firms set tighter internal limits (RSD ≤5%, 95–105%) [78,79].

- **Moisture content**

The water content plays an important role in the control of SD performance and stability. The high degree of water holding, particularly in conditions of high relative humidity, is largely due to the inherent hygroscopic nature of most of the common polymer carriers in such formulations. Water uptake depends on the polymer concentration and atmospheric humidity, and attains equilibrium within different time periods based on these factors. The absorbed water can cause unwanted modifications of the SD, that is, the occurrence of such phase changes as recrystallisation of the amorphous form of the drug. These changes are better suited to occur in stressful conditions, i.e., high temperature and humidity, and have the capabilities of compromising the physical stability and dissolution benefit of the formulation. It is on this basis that the water exposures have to be controlled to ensure the amorphous shape, the long-term stability, and the SD reliability [80].

Measurement of SD moisture content is a quality control property of significant importance, as high water content can influence the physical stability, drug release properties, and glass transition temperature (Tg) of the drug product. A number of analytical techniques are widely used to quantify the moisture content. The most ancient one is Loss on Drying (LOD), according to which the sample undergoes dry-weighing and is subsequently heated (usually at 105 °C), and a loss in weight is considered to be caused by water and volatile substances. LOD cannot distinguish water and other volatiles, even though it is not difficult. A more precise and quantitative measure of water can be obtained by Karl Fischer titration, which is the gold standard of measuring traces of moisture in solid and liquid material by carrying out a redox titration reaction that is selective to water. As a rapid method of non-destructive analysis, NIR spectroscopy is used more often in the analysis of pharmaceuticals to determine the moisture content. NIR makes the common O–H vibrational overtones, and off-line and in-process testing of moisture in solid dosage forms can be carried out without sample preparation. This is needed in ensuring that the ingredients of moisture are maintained at a moderate level to avoid recrystallisation or decomposition of the amorphous drug in the dispersion matrix [81–83]. The question of the proper method to employ will depend on the sensitivity required, the availability of other volatile substances, and the real-time or endpoint measurements required.

**Acceptance criteria:** Typical limit ≤2.0% w/w (Karl Fischer). For low-$T_g$ or hygroscopic systems, ≤1.0% or ≤0.5% may be required. Moisture control is critical to avoid plasticization and crystallization [84].

- **Stability study**

Time dependence of resistance to crystallisation. Stability tests would be applied to ascertain long-term physical stability of amorphous solid dispersion (ASDs), i.e., whether they resist crystallisation or not. One of the most important factors for such stability is miscibility between the APIs and the polymeric carrier system. Such miscible systems that form a drug as a homogeneous dispersal of molecular entities in the polymer matrix should be far more physically stable. Part of this increased stability is due, at least, to the lower mobility of the molecules and to the high concentrations of intermolecular interaction which hamper the nucleation and the crystal growth. Recrystallisation of the drug and polymer will tend to take place in the phase-separated systems where the drug and polymer are not perfectly miscible, and the length of the recrystallisation is relatively low and tends to fall within a finite time period.

More sophisticated characterisation instruments, including X-ray powder diffraction (XRPD) and predictive modelling based on structure, are employed routinely to evaluate and track the solid-state char-

acteristics of ASDs. The methods enable one to sense the amorphous character of the system and the onset of crystallisation. In the end, success and preservation of high miscibility in SD are directly necessary in order to provide the physical stability and preserve the enhanced solubility and bioavailability advantages of the amorphous state [85].

**Acceptance criteria:** According to ICH Q1A(R2):

- **Physical:** No crystallization (or ≤1–5% increase) by XRPD/mDSC.

**Chemical:** Assay 90–110%; total impurities ≤1.0–2.0%; single unspecified ≤0.2%; genotoxic impurities per ICH M7. Specifications must be met after long-term and accelerated storage [86].

- **Solubility study**

SD technology is one of the most extensively researched techniques for the improvement of the solubility and rate of dissolution of poorly water-soluble drugs, especially for BCS Class II type drugs. They are low in aqueous solubility but high in membrane permeability; thus, their solubility, as opposed to absorption, is rate-limiting. SD act by drug dispersion within a hydrophilic or amphiphilic carrier matrix, enhancing wettability, decreasing particle size, and overall converting the drug into a more soluble amorphous state.

Solubility is explored in SD by measuring the extent to which the formulation enhances drug solubility under different physiological pH levels. Methods like binary and ternary SD systems are generally contrasted, the latter containing extra surfactants or polymers to facilitate further solubilization. The performance of these types of systems is usually evaluated by analytical methods like Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), and differential scanning calorimetry (DSC), which validate amorphisation and molecular interactions between the drug and carrier [87].

Increased solubility is directly proportional to increased dissolution rates, resulting in positive oral bioavailability. Furthermore, proper carrier selection will reduce gastric irritation and enhance drug tolerance. For the most part, SD is a viable formulation strategy to mitigate solubility issues of most APIs [3,88].

**Acceptance criteria:** Typically set during development:

- Achieve target supersaturated concentration (e.g., ≥X μg/mL) in biorelevant media within 15 min.
- Apparent solubility ≥2–10× higher than crystalline drug.

No rapid precipitation; %RSD ≤10% across replicates [89].

*3.6 Characterization of* SDs

- **Fourier Transform Infrared Spectroscopy (FTIR)**

Fourier Transform Infrared Spectroscopy **(**FTIR) has been extensively utilised in the detection of intermolecular interactions, including the hydrogen bonding of drugs and excipients. The appearance of interactions stabilising the amorphous form and preventing crystallisation is confirmed by shifts in characteristic functional group vibrations. As an illustration, FTIR data of the carbamazepine –Kollidon ® VA64 –Neusilin® UFL2 TSDs indicated band shifts indicating hydrogen bonding between the ingredients [68,90].

- **Differential Scanning Calorimetry (DSC)**

DSC recognises thermal transitions, which are the Tg and the melting points. A Tg of one means that the drug and carrier are miscible, whereas the shift of Tg may suggest interactions. In the works of Fung et al. TSDs with ketoconazole and organic acids, oxalic and citric acid, have higher Tg values and lower crystallisation propensities, which validate increased stability [91,92].

- **Powder X-ray Diffraction (PXRD)**

Powder X-ray Diffraction (PXRD) is required to distinguish amorphous forms and crystalline forms. Amorphous drugs have halo patterns, and crystalline drugs have sharp peaks. The outcome of PXRD of itraconazole confirmed the amorphisation of the itraconazole in ternary solid dispersion (TSDs) according to the results of Janssens et al. using TPGS 1000 and PVP-VA64 [93,94].

- **Polarising Light Microscopy (PLM)**

Polarising Light Microscopy (PLM) identifies transitions of crystalline morphology and polymorphs. The amorphous conversion is visually confirmed with the help of it, in addition to DSC and PXRD. PLM observed polymorphic changes in TSDs made with carbamazepines, which were associated with storage and formulation conditions [90].

- **Thermogravimetric Analysis (TGA)**

Thermogravimetric Analysis **(**TGA) measures the stability of the thermal and the content of the solvent remaining by the weight loss. Indicatively, TGA thermograms of febuxostat TSDs showed changes in the degradation temperature, which implies increased thermal stability [95].

- **Solid-State Nuclear Magnetic Resonance (ssNMR)**

Solid-State Nuclear Magnetic Resonance (ssNMR) determines the interactions on the atomic level and establishes amorphisation. Hanada et al. have reported broad peaks in the 13C NMR spectra of probucol TSDs, downfield shifts, which confirm hydrogen bonding to PVP and the amorphous state [96,97].

- **Dielectric Spectroscopy**

It determines the motion of molecules by measuring the time of α -relaxation. There is less mobility, which indicates high molecular stability. Li et al. have shown a much slower mobility of SMZ-TMP ternary ASDs than binary systems, implying a higher level of stability [98].

- **Scanning electron microscopy (SEM)**

The morphology, surface features, and particle size are displayed in SEM images. The smaller and more spherical size of spray-dried ketoconazole TSDs containing PVP, organic acids, and other dissolution enhancers was observed as an example [98].

*3.7 Role of SDs in Solubility Enhancement*

- **Amorphization of the Drug**

Transposition into amorphous form stage raises the solubility of a drug. Transformation of the drug from the well-structured crystal form to the amorphous form increases the free energy of the drug; therefore, forces to form the strong intermolecular interactions that take place in crystalline structures are not accessible in amorphous drugs and hence, dissolve readily. Accordingly, the rate of dissolution and bioavailability of the drug is increased [99].

Subjects of SD are typically transformed into an amorphous form, and amorphous materials have a higher free energy and movement. The amorphous compound is more soluble in the gastrointestinal fluids as compared to the crystalline counterpart, resulting in an apparent increased solubility and dissolution rate [100].

- **Improved Wetting and Dispersibility**

With SDs, hydrophilic carriers (e.g., PVP, HPMC) are applied in order to enhance the wettability of the drug and decrease the interfacial tension between the drug particles and the dissolution media in order to obtain improved solubility [48].

Enhanced dispersibility and wetting play an important role in the formulation of the solubility of poorly water-soluble drugs. The more the drug is wettable, the more it will come in contact with the body fluid, resulting in a smaller contact angle and quicker dissolution. This particularly holds in the event of hydrophobic drugs [101].

Dispersibility spreads out the uniformly dispersed drug particles in the medium to avoid agglomeration and allows the achievement of uniform dissolution. Tiny particles that are well dispersed possess more surface area, which is in contact with the solvent, and this enhances the dissolution process. The wetting and dispersion enhancement is usually done through the application of surfactants, hydrophilic carriers, and SD techniques, thereby leading to an increase in bioavailability and therapeutic activity [101].

- **Particle Size Reduction**

A decrease in particle size improves the solubility of a drug, as the small particle size has an increased surface area, therefore, having a greater ability to interact with the solvent. The smaller the particle size, the higher the rate of dissolution of a drug because they have more surface area with which it can react with the dissolving agent in the environment. Noyes-Whitney equation, which states that the rate of dissolution is proportional to surface area. In addition to that, smaller particles are associated with

a greater dissolution pressure that facilitates faster dissolution and absorption in the GI tract. Some of the methods applied in enhancing solubility and bioavailability of poorly soluble drugs include micronisation and nanosuspension formulation [102].

Many preparation methods (e.g., spray drying, hot-melt extrusion) result in fine drug particles or even molecular dispersion of the drug within the carrier. Smaller particle sizes mean greater surface area, which enhances the dissolution rate [103].

- **Inhibition of Drug Precipitation**

Some SDs maintain a supersaturated drug concentration in the gastrointestinal tract. The polymer matrix can inhibit nucleation and crystal growth, preventing the drug from precipitating back into its poorly soluble crystalline form [50].

Avoiding the precipitation of the drugs can also help in the enhancement of solubility by maintaining the drugs in a supersaturated condition, which enhances drug absorption and bioavailability. Supersaturable formulations can result in transiently elevated (normal solubility limit of) drug concentration, but without a stabilizing mechanism, this supersaturated state collapses and leads to precipitated ineffective drug [104].

*3.8 Improvement of Bioavailability Using SDs*

This is occurred by:

- **Enhancing the solubility of the drugs**

SDs enhance the solubility of the drugs in different ways, which leads to the enhancement of permeability 105.

When a drug's solubility increases, it will increase the bioavailability of the drug; the bioavailability is the part of a drug that gets into circulation and hence can cause a therapeutic effect. Poorly soluble drugs tend to dissolve slowly; hence, their absorption in the gastrointestinal tract remains incomplete. Such unnatural solubility by decreasing particle size, complex formation, or using surfactants may make the drug more soluble for biological fluids and hence available for absorption. This results in higher concentration of the drug in plasma, lower doses, and better therapeutic response [102].

- **Enhanced Permeability and reduced efflux**

SD enhances the bioavailability of poorly water-soluble drugs, particularly BCS-Class II drugs with low solubility but high permeability, by improving both dissolution and permeability across biological membranes. This technique disperses a hydrophobic drug within a hydrophilic carrier matrix, which may be crystalline or amorphous, to increase the drug's effective surface area, wettability, and dispersibility while often converting the drug to an amorphous form, all of which promote better permeation through biological membranes. Enhanced permeability directly increases bioavailability by allowing more drug to cross the gastrointestinal membrane into circulation, overcoming a barrier to absorption. For example, a SD of nitrendipine using silica particles as a carrier, prepared via a melt-mixing method, exhibited significantly improved dissolution properties compared to its crystalline form, facilitating greater membrane permeation and absorption. [106].

In TSDs, the inclusion of surfactants (e.g., TPGS, poloxamer) or alkalizing agents may increase membrane permeability or reduce efflux (e.g., P-glycoprotein inhibition), improving bioavailability 107,108.

- **Prolong supersaturation**

SD polymers stabilise supersaturation by creating molecular interactions with the drug, decreasing molecular mobility, and generating an interfacial barrier around drug particles. The sum effect inhibits or stops crystallisation and LLPS, prolonging the period of the supersaturated state throughout dissolution. Consequently, more drug is in solution at a higher concentration for an extended period, enabling better absorption in the gastrointestinal tract [109].

The performance of SDs to sustain supersaturation is commonly assessed by in vitro dissolution and supersaturation experiments, and analytical methods like FTIR, XRD, and SEM for tracking physical state and drug–polymer interaction. Though supersaturation is required for enhanced solubility and dissolution, enhancing bioavailability depends on drug permeability since the latter does not ensure favourable absorption [109]

*3.9 Improvement of Stability Using* SDs

SDs, particularly amorphous SDs, achieve better physical stability for poorly water-soluble drugs by embedding them in polymeric matrices, which restrict crystallisation and phase separation. Lin X et. al. (2018) demonstrates ASD stability mechanisms by exploring three main aspects: thermodynamic principles, alongside kinetics and environmental factors. The combination of drug and polymer maintains thermodynamic stability through perfect miscibility while staying below the drug's solubility threshold in the polymer matrix to stop spontaneous recrystallisation. The stability of ASDs improves through the use of polymers with high Tg that decrease drug molecular mobility and by developing strong drug-polymer interactions through hydrogen bonding or acid-base mechanisms that restrict molecular motion. The selection of hot-melt extrusion or spray drying as manufacturing methods will affect supersaturation levels, which directly affect the physical stability of the product. Temperature and humidity conditions significantly impact stability as elevated temperature enhances molecular mobility while high humidity affects drug-polymer interactions and promotes moisture-induced recrystallisation. To protect ASDs from moisture exposure, hydrophobic polymers and protective polymer blends serve as effective shields against these effects. The SDs achieve drug amorphous state preservation through these mechanisms, which significantly increase their storage and handling stability [110].

## 4. Advantages and disadvantages of SDs

The advantages and disadvantages of solid dispersion are shown in Table 3.

## 5. Conclusion

Solid dispersion technology has become an important strategy in oral drug delivery, particularly for poorly water-soluble drugs. It enhances drug solubility and dissolution rate, leading to improved bioavailability. These improvements are mainly achieved through drug amorphization, enhanced wettability, and inhibition of recrystallisation. In addition, advanced analytical techniques ensure proper characterization and quality evaluation of solid dispersion systems.

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