

Solid Dispersion-Based Approaches for Improving Oral Bioavailability: Current Progress and Future Perspectives

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Publication Date: 2025/08/01

Abstract: Poor water solubility remains a key challenge in the oral delivery of many active pharmaceutical ingredients (APIs), particularly those in BCS Class II and IV, often resulting in low bioavailability and limited therapeutic effect. Solid dispersion (SD) technology has gained widespread attention as a practical and effective solution to this issue by improving solubility and dissolution rates. This review outlines recent developments in SD systems, including novel carriers, advanced techniques like hot-melt extrusion and spray drying, and polymer innovations that support stable amorphous drug formulations. It also covers SD classification, analytical methods such as DSC and TMDSC, and the mechanisms behind enhanced drug absorption. Overall, solid dispersions are emphasized as a flexible, efficient, and commercially promising approach to boost the oral bioavailability of poorly soluble APIs.

Keywords: Solid Dispersion, Bioavailability Enhancement, Amorphous Drug, Surfactant, Solubility Improvement.

How to Cite: Dr. Gayathri Rajaram; Charan Prakash Krishnan; Monika Sekar; Tamil Selvi Sriraman (2025) Solid Dispersion-Based Approaches for Improving Oral Bioavailability: Current Progress and Future Perspectives.

International Journal of Innovative Science and Research Technology,
10(7), 2624-2631. <https://doi.org/10.38124/ijisrt/25jul1184>

I. INTRODUCTION

Poorly water-soluble drugs typically exhibit low oral bioavailability because limited solubility hinders their absorption in the gastrointestinal tract, ultimately affecting therapeutic effectiveness. Formulation challenges arise from low aqueous solubility because insufficient dissolution in GI fluids generally leads to reduced bioavailability.

To overcome these limitations, the Biopharmaceutics Classification System (BCS) provides a scientific model for categorizing drugs based on their solubility and intestinal permeability, which helps inform formulation strategies. Various methods are employed to enhance solubility, including prodrug formation, salt conversion, particle size reduction, use of solid dispersions with hydrophilic carriers, and converting crystalline drugs into amorphous forms. Amorphous forms, which lack the ordered molecular structure of crystals, can be created by rapidly cooling a molten drug to prevent molecular rearrangement or by disrupting the crystalline lattice to introduce structural defect.⁴

Enhancing the solubility and dissolution of poorly water-soluble drugs is a major challenge in drug development, leading to the use of various scalable and cost-effective methods. A common approach is particle size reduction, particularly in solid dispersion systems,¹ to increase surface area. While micronization can improve dissolution for drugs with dissolution-rate-limited absorption, it may also cause particle agglomeration, reducing wettability. To counter this, surfactants are frequently added to formulations to boost the solubility and wettability of hydrophobic drugs.³ An example is the liquisolid technique, where a drug dissolved in a non-volatile solvent is adsorbed onto inert, insoluble carriers.²

The Noyes-Whitney equation describes the dissolution rate and highlights essential factors that can be adjusted to enhance the bioavailability of poorly soluble drugs.

$$dc/dt = A.D.(C_s - C)/h$$

The rate at which a drug dissolves (dc/dt) is directly proportional to the surface area of the drug (A), the diffusion coefficient (D), and the concentration gradient between the

saturation solubility (C_s) and the drug concentration in the bulk solution (C), and inversely proportional to the thickness of the diffusion layer (h).⁵

Among the most promising strategies is solid dispersion is a technique in which hydrophobic drugs are distributed within a hydrophilic carrier in solid form, using methods such as melting, solvent evaporation, or a combination of both, leading to the formation of a hydrophilic matrix containing the hydrophobic drug.¹

The concept of solid dispersions was first proposed by Sekiguchi and Obi in 1961 to improve the dissolution and oral absorption of poorly water-soluble drugs, and was further developed by Mayerson and Gibaldi in 1966. Later, in 1971, Chiou and Riegelman defined solid dispersions as the incorporation of active pharmaceutical ingredients into an inert carrier matrix using techniques like melting, solvent

evaporation, or their combination. The term "solid dispersion" refers to a dosage form in which the drug is evenly dispersed within a carrier matrix to enhance its oral bioavailability.⁵

However, the most efficient method involves enhancing solubility using formulation strategies such as polymorphs, nanosuspensions, pseudo polymorphs (solvates), cyclodextrins, eutectic mixtures, non-molecular solid dispersions, soluble prodrugs, and salt formation.⁶ This review highlights current strategies for improving the solubility and oral bioavailability of poorly water-soluble drugs, with a focus on solid dispersion systems as a practical and effective solution in pharmaceutical development.

The types of Solid Dispersions are represented in Figure 1.

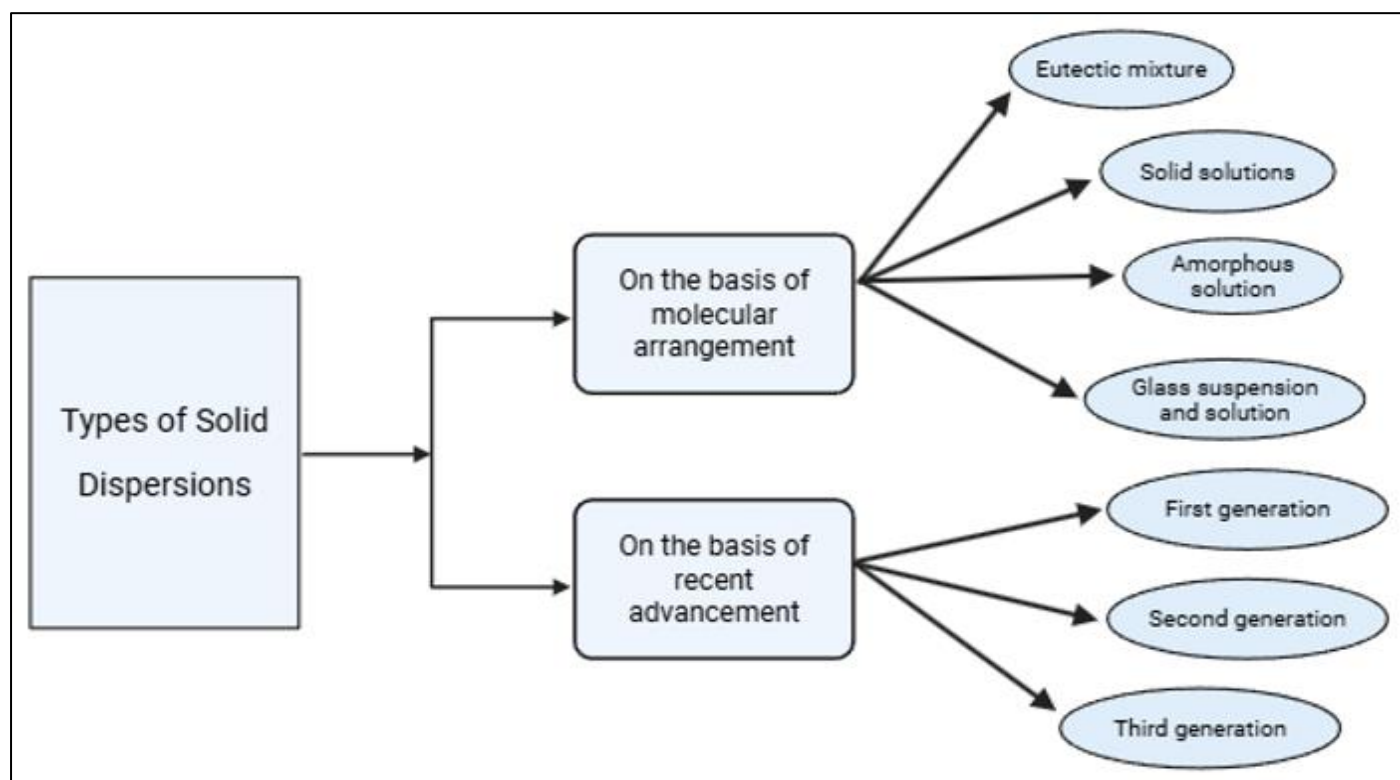


Fig 1 Types of Solid Dispersion

II. CLASSIFICATION OF SOLID DISPERSION

A. Solid Dispersions can be Classified into the Following Types

➤ Based on their Molecular Arrangement¹

- **Eutectic mixtures-** These mixtures are typically produced by rapidly cooling a molten combination of two components, producing a finely crystalline structure.
- **Solid solutions-** It is further defined as two types:

➤ Based on Miscibility, it has Two Types

- **Continuous solid solutions-** In continuous solid solutions, the components are fully miscible, meaning the

intermolecular interactions between them are stronger than those within each separate substance.

- **Discontinuous solid solutions-** In this, the components exhibit only partial solubility in one another.

➤ Based on the Distribution of the Solvates

- **Substitutional crystalline solution-** In such solid solutions, solute molecules replace solvent molecules within the crystalline lattice structure.
- **Interstitial crystalline solid solution-** In these solid solutions, dissolved molecules occupy the voids or interstitial spaces within the crystal lattice.

- ✓ **Amorphous solid solution-** In amorphous solid solutions, solute molecules are uniformly dispersed at the molecular scale but lack an ordered structure within the amorphous solvent.
- ✓ **Glass solutions and glass suspensions-** A glass solution is a uniform system in which the solute is evenly dispersed at the molecular level within a glassy solvent. This glassy state is characterized by its brittle texture and transparency when kept below the glass transition temperature. The term "glass" can refer to either a single

pure substance or a combination of pure substances in this specific physical state.

➤ *Based Upon Recent Advancement⁷*

Novel manufacturing techniques have been developed to overcome earlier limitations, and this work highlights recent progress along with the classification of solid dispersions according to their preparation methods.⁸ The generations of Solid dispersions are represented in Figure 2.

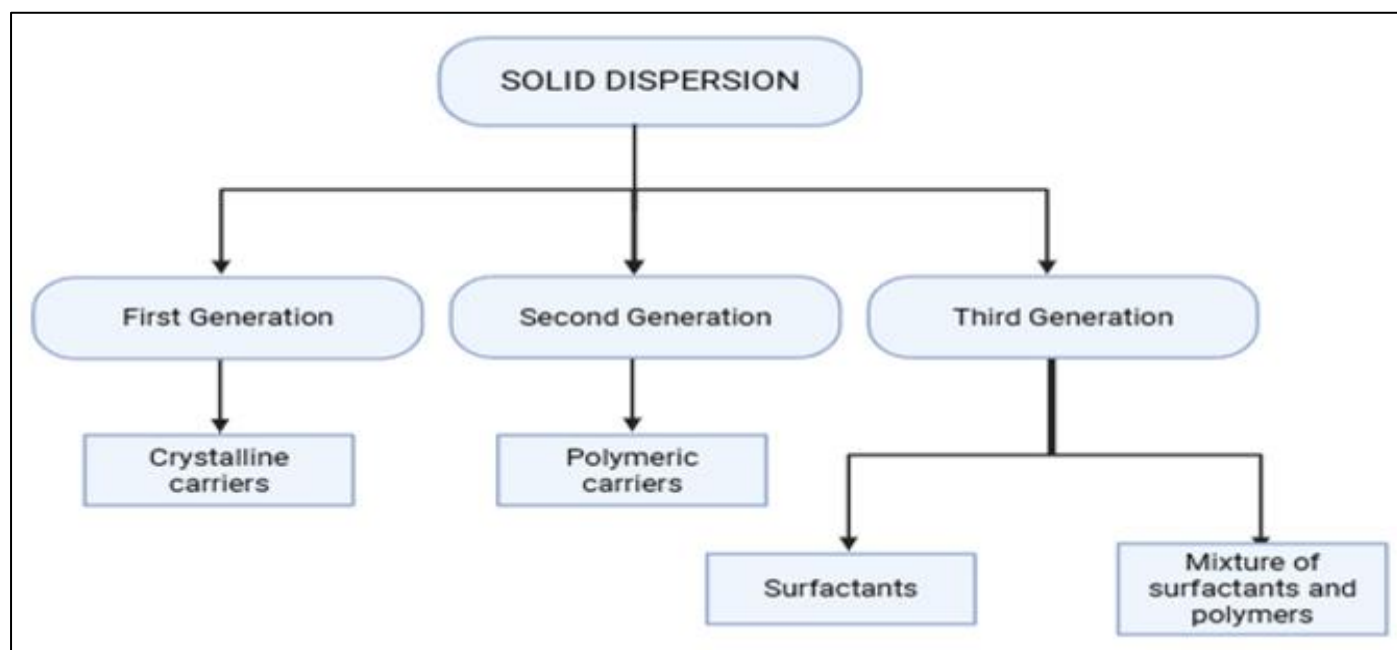


Fig 2 Flow Chart Representation of 3 Generations of Solid Dispersion.

- **First generation solid dispersion-**First-generation solid dispersions used crystalline carriers like urea and sugars to enhance drug release, but they were thermodynamically unstable and less effective. Introduced by Sekiguchi and Obi in 1961, this concept improved drug bioavailability through eutectic mixtures. Early formulations with urea and later with mannitol showed enhanced drug release due to reduced particle size, better wettability, and faster carrier dissolution. However, these crystalline carriers still had slower drug release than later amorphous systems.⁹
- **Second generation solid dispersion-**Second-generation solid dispersions use amorphous polymeric carriers that evenly distribute the drug at the molecular level, offering improved solubility and bioavailability over crystalline systems. Developed after discovering the limitations of crystalline carriers in the late 1960s, these dispersions utilize synthetic (e.g., PEG, povidone) or natural (e.g., HPMC, cyclodextrins) polymers. They are classified as solid solutions (homogeneous mixtures), solid suspensions (two-phase systems), or mixed systems. These formulations enhance drug wettability, reduce particle size to the molecular level, and form amorphous drug states, with the carrier playing a key role in controlling drug release.⁹
- **Third generation solid dispersion-** Third-generation solid dispersions incorporate surfactants or combinations of amorphous polymers and surfactants to enhance the

bioavailability of poorly soluble drugs. These systems improve dissolution, inhibit recrystallization, and maintain polymorphic purity. Common surfactants include inulin, poloxamer 407, gelucire 44/14, and others. Combining surfactants with polymers has shown significant results—such as LAB68, where PEG and polysorbate 80 boosted bioavailability tenfold and ensured 16-month stability. Similar combinations improved the dispersion of drugs like felodipine. Surfactants also help prevent drug precipitation and particle agglomeration.⁹

➤ *Advantages of Solid Dispersion*

- **Improved Bioavailability:** By reducing particle size and increasing surface area, solid dispersions enhance dissolution and bioavailability.¹⁰
- **Enhanced Wettability:** Carriers improve drug wettability, boosting solubility and absorption.¹¹
- **Amorphous State Advantage:** Drugs exist in a metastable, amorphous form, leading to higher solubility.¹²
- **Better than Salt Formation:** Solid dispersions are simpler and more effective for solubility enhancement than salt formation.¹³
- **Preferred for Oral Dosage Forms:** They allow formulation of solid oral doses rather than liquids, unlike solubilized

forms, though ultra-fine powders may have poor mechanical strength and handling issues.¹⁴

➤ *Disadvantages of Solid Dispersion*¹⁵

- **Instability Over Time:** Changes in crystallinity can occur, reducing the drug's dissolution rate.
- **Temperature and Moisture Sensitivity:** Solid dispersions are more prone to degradation than physical mixtures.
- **Handling Issues:** Tackiness can make them difficult to process and handle.
- **Limited Commercial Use:** Crystallization risks during manufacturing or storage (due to mechanical, thermal, or humidity stress) hinder large-scale application.¹⁶
- **Moisture Absorption by Polymers:** Can lead to phase separation, crystallization, crystal growth, or conversion to a stable crystalline form—ultimately reducing solubility and dissolution.¹⁷

➤ *Limitations Include*

- Time-consuming and preparation method is expensive,
- Consistency of physicochemical properties,
- Challenges in integrating into dosage formulations and
- Challenges in scaling up manufacturing and ensuring drug and vehicle stability.

III. METHODS FOR DEVELOPMENT OF SOLID DISPERSION

➤ *Solvent Evaporation Method:*

The solvent evaporation method, developed after the melting technique, involves dissolving both drug and carrier

in a common solvent, followed by solvent removal under vacuum to form solid solutions. This avoids thermal degradation due to the low evaporation temperature of solvents. Examples include indomethacin with ethyl cellulose and HPMC, and β -carotene with PVP. Griseofulvin-PVP dispersions made this way showed a 5–11-fold increase in release rate compared to the micronized drug. Bates first coined the term "coprecipitates" for dispersions made by this method.^{18, 19, 20}

➤ *Co-Precipitation Method:*

The co-precipitation method enhances the solubility and bioavailability of poorly water-soluble drugs by simultaneously precipitating the drug and carrier from a shared solution, ensuring uniform dispersion. The drug is dissolved in a carrier solution under stirring and protected from light. Precipitate is vacuum filtered and dried at room temperature to preserve structural water. This technique uses differences in solubility between the drug, carrier, organic solvent, and anti-solvent to induce rapid precipitation and form a solid dispersion.²¹

➤ *Melting Method:*

The melting (fusion) method involves heating the drug and a water-soluble carrier until melted, then rapidly cooling the mixture to form a solid dispersion. The solid is then crushed, ground, and sieved for use. To prevent thermal degradation, the process can be conducted in sealed vessels, under vacuum, or in an inert gas atmosphere like nitrogen. Rapid cooling methods, such as ice baths or spreading on cool surfaces, promote supersaturation, fine crystallite formation, especially in eutectic mixtures. However, heat-sensitive drugs or carriers may degrade, so precautions are necessary.²² Ex: Albendazole and urea solid dispersion.

Table 1 Comparison of Melt Method vs Co-Precipitation vs Solvent Evaporation for Solid Dispersion

Factor	Solvent evaporation method	Co-precipitation method	Melting method
Usage of solvent	No solvents required	Requires organic/ aqueous solvents	Requires organic solvents
Thermal stability	Unsuitable for drugs that are sensitive to heat	Suitable for most drugs	Suitable for most drugs
Process complexity	Simple, fewer steps	Complex due to solvent removal	Moderate complexity
Energy consumption	High	Moderate	High
Risk of phase separation	High if cooling is not controlled	Low	Moderate
Drug loading capacity	Moderate to high	Moderate	High
Environment impact	Low	High	High
Final product properties	Fine dispersion but risk of drug recrystallization	Molecularly dispersed drug, good stability	Requires proper solvent removal to avoid crystallization

➤ *Co-Grinding Method:*

The kneading method is a solvent-free mechanical technique where a drug and hydrophilic polymer carrier are co-ground to enhance solubility and dissolution. Mechanical force disperses the drug at a molecular or microcrystalline level, improving wettability, surface area, and potentially inducing amorphization. The drug and carrier are first blended, then ground in a vibratory ball mill with steel balls, and the resulting fine powder is stored for later use.²³ Ex. Solid dispersion of chlorthalidone and mannitol was developed using this method.

➤ *Gel Entrapment Technique:*

Gel entrapment is a technique where a drug is embedded in a polymeric gel matrix, enhancing its solubility and dissolution. The drug is dispersed within a gel—typically made from hydroxypropyl methylcellulose in an organic solvent—and mixed via sonication. After solvent removal through vacuum evaporation, a solid matrix forms, trapping the drug in an amorphous or finely crystalline state. The final product is ground and sieved to reduce particle size.²⁴

➤ *Spray Drying Method:*

Spray drying is a solvent-based method where the drug and carrier are co-dissolved and sprayed into hot air, rapidly drying into solid dispersions. This process disperses the drug at the molecular level within the polymer, maintaining it in an amorphous or nano-sized form and preventing crystallization. The drug is dissolved in a suitable solvent, the carrier in water, and the solutions are combined—often by sonication—before spray drying.³

➤ *Lyophilization Technique:*

Lyophilization, or freeze-drying, is a solvent-based method where the drug and carrier are co-dissolved, frozen, and dried by sublimation under vacuum to form a solid dispersion. This technique enables molecular-level mixing, enhances solubility and stability of poorly water-soluble drugs, and serves as an alternative to solvent evaporation methods.²⁵

➤ *Electrospinning Method:*

Electrospinning is a nanotechnology-based solid dispersion technique used to enhance the solubility of poorly water-soluble drugs. It involves applying high voltage (5–30 kV) to a drug-polymer solution or melt, creating charged jets that form nanofibers as the solvent evaporates. These fibers are collected as a nonwoven mat. The process depends on factors like viscosity, feed rate, surface tension, and voltage, with a Taylor cone forming at the nozzle tip. Electrospinning is simple, cost-effective, and effective for controlled drug release and molecular-level dispersion.²⁶

➤ *Dropping Method Solution:*

The dropping method is a solvent-free technique used to produce spherical solid dispersion particles by dropping a molten drug-carrier mixture onto a flat surface, where it rapidly solidifies. Initially developed for crystallization, it now offers a simpler alternative to traditional methods, improving dissolution rates without using solvents. Carriers that solidify at room temperature enhance efficiency, and the method is ideal for streamlined, lab-scale production.²⁶

➤ *Melt-Extrusion Method:*

Hot-melt extrusion is a widely used technique for forming solid dispersions by melting and blending an API with a carrier (typically around 40% w/w drug) using a co-rotating twin-screw extruder. The mixture is processed for about one minute at elevated temperatures, making it suitable for moderately heat-sensitive drugs. This method produces various dosage forms like pellets, granules, tablets, and powders, offering uniform dispersion and enhanced drug solubility.²⁷

➤ *Melt Agglomeration Process:*

This technique forms solid dispersions using a binder as the carrier, either by:

- Heating a mixture of binder, drug, and excipients above the binder's melting point, or
- Spraying molten, drug-loaded binder onto preheated excipients using a high-shear mixer.

Both methods enhance drug dispersion and solubility.

➤ *Kneading Method:*

Kneading is a simple and effective method for preparing solid dispersions, ideal for heat-sensitive drugs. It uses minimal solvent, typically an alcohol-water (1:1) mixture, to blend and grind the drug with a carrier into a paste. This is kneaded for 45–60 minutes, then dried at 45 °C, pulverized, and sieved. The method operates at low temperatures, minimizes solvent use, and reduces the risk of thermal degradation.²⁸

IV. CARRIERS USED IN SOLID DISPERSION

➤ *Polyethylene Glycol (PEG):*

Polyethylene glycols (PEGs) are widely used carriers in solid dispersions, typically with molecular weights between 1,500 and 20,000. Their physical form varies by MW, from liquids to waxy solids and hard crystals. PEGs have good water and organic solvent solubility, low melting points (under 65°C), and enhance drug solubility and wettability. For example, PEG 6000 significantly improves the dissolution rate of moderately soluble drugs like aspirin.²⁹

➤ *Polyvinylpyrrolidone (PVP):*

Polyvinylpyrrolidone (PVP) is a polymer used in solid dispersions, with molecular weights ranging from 2,500 to 3,000,000 and classified by K values. Due to high glass transition temperatures (e.g., PVP K25 at 155°C), it is better suited for solvent-based methods rather than hot melt techniques. PVP enhances drug wetting and dissolution, but higher molecular weight grades have lower water solubility and higher viscosity, which can slow drug release—evident in the slower dissolution of indomethacin from PVP K90 compared to K12.^{30,31}

➤ *Cellulose Derivatives³²*

• *Hydroxypropyl Methylcellulose (HPMC):*

Hydroxypropyl methylcellulose (HPMC) is a modified cellulose polymer with methyl and hydroxypropyl substitutions, such as in HPMC Type 2910. With molecular weights ranging from 10,000 to 1.5 million, HPMC is soluble in water and solvent mixtures. In solid dispersions, it enhances drug release, particularly for poorly soluble weak acids—e.g., Nifedipine shows improved release when formulated with HPMC.

• *Hydroxypropyl Cellulose (HPC):*

Hydroxypropyl cellulose (HPC) is a versatile polymer with good solubility in water (up to ~40°C) and organic solvents like ethanol, methanol, and chloroform. Its molecular weight ranges from 37,000 (Type SSL) to 1,150,000 (Type H). Studies, such as by Yuasa et al., show that both polymer chain length and HPC concentration significantly influence drug release, as demonstrated with flurbiprofen.

• *Carboxymethylethylcellulose (CMEC):*

Carboxymethylethyl cellulose (CMEC) is a cellulose ether known for its acid resistance, remaining undissolved in

gastric conditions but dissolving rapidly above pH 5–6. It is also soluble in various organic solvents. In amorphous solid dispersions with drugs like nifedipine and spironolactone, CMEC significantly enhances dissolution at pH 6.8, making it ideal for targeted intestinal drug delivery.

➤ *Hydroxypropyl Methylcellulose Phthalate (HPMCP):*

Hydroxypropyl methylcellulose phthalates (HPMCPs) are cellulose esters used as enteric coatings, dissolving at pH 5–5.5 depending on the grade (HP 50 or HP 55). With molecular weights from 20,000 to 2,000,000, they vary in organic solvent solubility. In solid dispersions, HPMCPs significantly enhance drug dissolution—e.g., griseofulvin shows improved release at pH 6.8, and MFB-1041 dissolves 12.5 times faster when spray-dried with HP 55.

➤ *Polyacrylates and Polymethacrylates:*

Eudragits are glass-like polymers derived from acrylic and methacrylic acids, used in pharmaceuticals to control drug release. Eudragit E dissolves below pH 5 and enhances drug release, as seen with improved Benipidine dissolution. Eudragit L, which prevents stomach release, significantly boosts drug dissolution at pH 6.8, as demonstrated with griseofulvin and spironolactone.³³

➤ *Urea:*

Urea is a water-soluble, non-toxic compound used in early solid dispersion studies to enhance drug absorption. It improves drug release, as seen with sulphathiazole in rabbits and ursodeoxycholic acid in hot melt dispersions. Urea also doubled phenytoin's dissolution rate, though PEG 6000 performed better for that drug.³³

➤ *Sugar, Polyols and their Polymers:*

Sugars and sugar-like compounds are highly water-soluble and safe but are generally less suitable as carriers for solid dispersions due to their high melting points and poor solubility in organic solvents. These properties limit their use in both hot melt and solvent-based methods. However, some, like mannitol, with a melting point of 165–168°C and stability up to 250°C, can be used in certain hot melt applications.³⁴

➤ *Organic Acids and their Derivatives:*

Organic acids such as succinic acid and citric acid have likewise been investigated as carriers in solid dispersion systems. They were first used with the goal of improving the dissolution rate of drugs such as Griseofulvin.

V. CHARACTERIZATION OF SOLID-DISPERSION

➤ *Powder X-ray Diffraction:*

Powder X-ray diffraction is a useful tool for checking if a material has a well-organized, long-range structure. The sharper the diffraction peaks, the higher the likelihood that the material is crystalline.

➤ *Infrared Spectroscopy:*

It detects drug-matrix interactions by analyzing energy patterns, with sharp vibrational bands indicating crystallinity. Fourier Transform Infrared Spectroscopy (FTIR) offers

greater precision and can measure crystallinity levels from 1% to 99%.³⁵

➤ *Water Vapour Sorption:*

Water vapor sorption can distinguish between amorphous and crystalline forms based on differences in moisture absorption, but requires accurate hygroscopic data for both forms to be effective.³⁶

➤ *Isothermal Microcalorimetry:*

Isothermal microcalorimetry measures the energy released during crystallization of amorphous materials above their glass transition temperature (T_g). Its limitations include requiring stable materials that crystallize only during measurement, assuming complete crystallization, and difficulty distinguishing energy contributions in mixtures of two amorphous substances like a drug and its carrier.³⁷

➤ *Dissolution Calorimetry:*

Dissolution calorimetry measures the amount of energy involved when a material dissolves, and this energy depends on whether the material is crystalline or amorphous. Typically, crystalline substances absorb heat when they dissolve (an endothermic process), while amorphous materials release heat during dissolution (an exothermic process).³⁸

➤ *Differential Scanning Calorimetry (DSC) and Temperature Modulated DSC (TMDSC):*

DSC and TMDSC are valuable techniques for characterizing solid dispersions. DSC measures thermal events to estimate crystallinity, while TMDSC, a more sensitive method, distinguishes reversible and irreversible transitions, helping assess drug miscibility and molecular dispersion. Together, they reveal the drug's physical state and distribution in solid dispersions.^{39, 40, 41}

➤ *Confocal Raman Spectroscopy:*

It assesses drug distribution in solid mixtures, with less than 10% variation indicating good homogeneity. However, its 2 μm³ resolution may miss nano-sized amorphous particles, introducing some uncertainty at smaller scales.

➤ *In Vitro Dissolution Studies:*

In vitro dissolution studies help predict a drug's bioavailability and bioequivalence through *in vitro-in vivo* correlation (IVIVC). However, for drugs with dissolution-limited absorption, especially in solid dispersions, *in vivo* studies are needed to accurately assess absorption and performance.⁴²

VI. RECENT ADVANCES AND FUTURE PERSPECTIVES

➤ *Fourth-Generation Solid Dispersions:*

Recent advances in solid dispersion technology focus on controlled-release systems that enhance solubility while enabling timed drug release. This is achieved by selecting suitable polymers and processing methods to precisely control drug release.

➤ *Nanotechnology Integration:*

Nanocrystal and nanocomposite solid dispersions combine multiple techniques to enhance both drug stability and dissolution, offering superior performance over traditional methods.

➤ *Stimuli-Responsive Solid Dispersions:*

These advanced systems are designed to release drugs only when they encounter certain triggers, such as changes in pH, temperature, or the presence of specific enzymes. This allows for more precise, targeted delivery of the medication.

➤ *Computational Approaches:*

Researchers now use molecular dynamics simulations and machine learning to predict drug-carrier compatibility and optimize formulations, reducing trial-and-error and speeding up development.

➤ *3D Printing of Solid Dispersions:*

Additive manufacturing, like 3D printing, is opening up new possibilities for creating personalized medications. It allows for custom doses, tailored release patterns, and intricate designs that traditional methods simply can't achieve.

VII. CONCLUSION

Solid dispersion technology has come a long way since it first began, becoming a powerful tool for tackling the common issue of poor drug solubility. The field is still growing, with exciting progress in new carrier materials, preparation techniques, and ways to study these systems. Although there are still hurdles—like maintaining stability and scaling up production—continuous research and innovation are steadily improving the potential and practicality of solid dispersions in drug development.

➤ *Conflict of Interest*

The author declares that there is no conflict of interest.

- **Funding Source:** None
- **Ethical Statements:** None

VIII. SUMMARY

The review highlights solid dispersion (SD) technology as an effective strategy to enhance the oral bioavailability of poorly water-soluble drugs by dispersing them in hydrophilic carriers, often in amorphous form. It covers various SD types, preparation methods, and carriers like PEG and PVP, along with characterization techniques. Recent innovations include nanotechnology, controlled-release systems, and computational tools. Despite some limitations, SDs remain a vital and evolving tool in improving drug solubility and therapeutic outcomes.

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