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Solid Dispersion Technology for Enhancement of Solubility and Bioavailability: A Comprehensive Review

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Abstract: ***Limited aqueous solubility remains a critical obstacle in the successful oral delivery of many therapeutic agents, particularly drugs categorized under Biopharmaceutics Classification System (BCS) class II and IV. Inadequate solubility leads to slow dissolution, insufficient gastrointestinal absorption, and poor oral bioavailability, ultimately compromising therapeutic effectiveness and contributing to variability in patient response. Solid dispersion (SD) technology has emerged as an effective and adaptable formulation approach to overcome these challenges without altering the chemical integrity of drug molecules. In SD systems, one or more active pharmaceutical ingredients are uniformly dispersed within hydrophilic carriers or polymeric matrices at the molecular or particulate level. This dispersion enhances drug wettability, reduces effective particle size, suppresses crystallinity, stabilizes amorphous forms, and significantly improves dissolution behavior. The present review provides an in-depth and systematic discussion of solid dispersion technology, encompassing its historical development, classification systems, formulation principles, preparation techniques, and characterization methods. In addition, the review highlights the underlying mechanisms responsible for solubility and bioavailability enhancement, pharmaceutical and industrial applications, stability considerations, regulatory requirements, scale-up challenges, recent advancements, and future perspectives.***

Keywords: Solid dispersion, solubility enhancement, bioavailability, amorphous solid dispersions, hydrophilic polymers, oral drug delivery

1. Introduction

Oral administration continues to be the most widely accepted route for drug delivery owing to its convenience, patient compliance, non-invasive nature, and economic advantages. Despite these benefits, 2 formulation scientists face persistent challenges in developing oral dosage forms for drugs with poor aqueous solubility. A substantial proportion of newly developed drug candidates exhibit low solubility, which directly affects dissolution rate and subsequent absorption in the gastrointestinal tract. According to the Biopharmaceutics Classification System (BCS), drugs belonging to class II and class IV are characterized by low solubility, making enhancement of dissolution and bioavailability a major formulation concern [1–4]. Poor solubility not only reduces the extent of drug absorption but also contributes to significant inter- and intra-patient variability, complicating dose optimization and therapeutic outcomes [5, 6]. Consequently, improving solubility has become a central objective in modern pharmaceutical development. Various formulation strategies, including micronization, salt formation, complexation, lipid- based systems, and particle engineering techniques, have been investigated to address solubility- related limitations [7–9]. Among these approaches, solid dispersion (SD) technology has gained considerable attention due to its simplicity, versatility, and effectiveness. By dispersing poorly soluble drugs within hydrophilic carriers or polymeric matrices at a molecular or finely divided state, SDs can markedly enhance dissolution rate, wettability, and intestinal absorption without modifying the drug's chemical structure [10–13]. This review aims to comprehensively summarize solid dispersion technology, emphasizing its evolution, formulation strategies, mechanisms of action, pharmaceutical relevance, and emerging trends in improving the solubility and bioavailability of poorly water-soluble drugs.

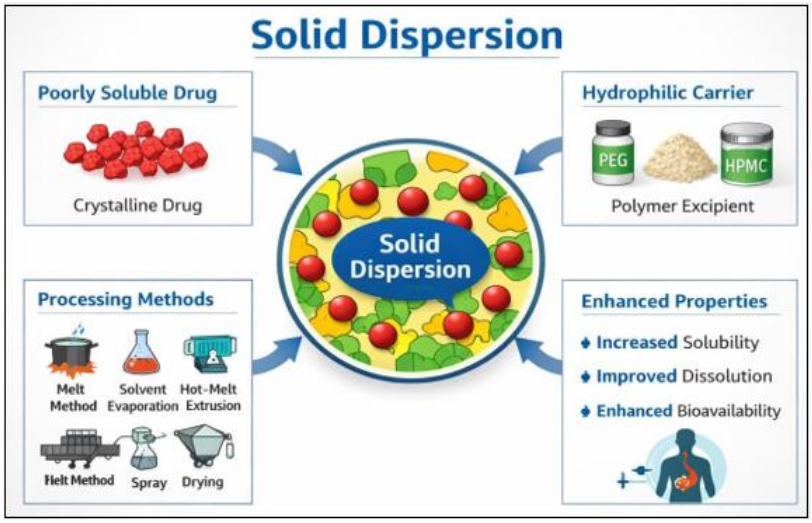

Figure 1: Schematic representation of solid dispersion technology

2. Historical Evolution of Solid Dispersion Technology

The origin of solid dispersion (SD) technology can be traced back to the early 1960s, when Sekiguchi and Obi first demonstrated that the dissolution rate of poorly water-soluble drugs could be enhanced by dispersing them in water-soluble carriers [2]. Their pioneering work introduced the concept of eutectic mixtures, prepared by melting the drug and carrier together followed by rapid solidification. These early formulations revealed that reduction in particle size and improved wettability were key contributors to enhanced dissolution behavior [1, 3]. During the 1970s and 1980s, research efforts expanded beyond eutectic systems to include amorphous solid dispersions and the use of hydrophilic polymers such as polyethylene glycol (PEG) and 3 polyvinylpyrrolidone (PVP). These polymers played a critical role in stabilizing drugs in an amorphous state, minimizing recrystallization, and further improving oral bioavailability [6, 11]. The 1990s marked a significant advancement in SD technology with the introduction of sophisticated manufacturing techniques such as hot-melt extrusion, spray drying, and co- precipitation. These methods enabled better control over drug distribution, improved uniformity, and enhanced scalability, making solid dispersions more suitable for industrial production [14– 16]. In recent years, solid dispersion technology has progressed from an experimental laboratory concept to a well-established and commercially successful formulation strategy. Several FDA- approved products now utilize solid dispersions to overcome solubility-related challenges and improve oral absorption [17–19]. Current research continues to focus on the development of advanced polymers and carrier systems capable of optimizing stability, dissolution performance, and therapeutic efficacy, thereby reinforcing the importance of solid dispersions in next- generation oral drug delivery systems [20–22].

3. Classification of Solid Dispersions

Solid dispersions (SDs) may be categorized using multiple criteria, including the molecular arrangement of the drug within the carrier, the nature of the carrier employed, and the method of preparation. Proper classification is essential for rational formulation design, as it aids in predicting physicochemical stability, dissolution behavior, and bioavailability performance of the resulting system [1, 3, 4].

3.1 Based on Molecular Arrangement of the Drug Eutectic Mixtures:

In eutectic solid dispersions, both the drug and carrier remain in a crystalline state and exist as a finely divided physical mixture. These systems melt at a temperature lower than the melting points of the individual components. Upon solidification, the drug is present as very small crystalline domains dispersed within the carrier, leading to improved dissolution primarily due to particle size reduction and enhanced wettability [2, 5].

Solid Solutions: Solid solutions are systems in which drug molecules are dispersed at the molecular level within the carrier matrix. Depending on the extent of solubility of the drug in the carrier, solid solutions are further classified into:

Continuous solid solutions: In these systems, drug molecules are uniformly distributed within the carrier lattice over a wide range of concentrations without phase separation. Discontinuous (partial) solid solutions: In this case, the drug is molecularly dispersed only up to a specific solubility limit, beyond which excess drug may exist as a separate phase [6, 7]. Amorphous Solid Dispersions (ASDs): Amorphous solid dispersions consist of drugs stabilized in a noncrystalline, amorphous form within polymeric carriers. The absence of long-range molecular order results in higher free energy and enhanced molecular mobility, leading to significantly improved apparent solubility and dissolution rates compared to crystalline forms [8–10].

3.2 Based on the Type of Carrier First-Generation Solid Dispersions:

First-generation SDs primarily utilize crystalline carriers such as urea and sugars and are generally based on eutectic mixtures. Although these systems demonstrate improved dissolution compared to pure drug, their practical application is limited due to poor physical stability and a high tendency toward recrystallization during storage [1, 3].

Second-Generation Solid Dispersions: Second-generation SDs employ amorphous polymeric carriers, including polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC). These carriers enhance drug solubility, improve dissolution rates, and provide better stabilization of the amorphous drug form, resulting in superior oral bioavailability [6, 11–13].

Third-Generation Solid Dispersions: Third-generation SDs incorporate surfactants or polymer– surfactant combinations in addition to hydrophilic polymers. The presence of surfactants improves wettability, enhances solubilization, and helps maintain drug supersaturation during dissolution, thereby leading to further improvements in oral bioavailability [14–16].

3.3 Based on Preparation Method Solid dispersions:

Based on Preparation Method Solid dispersions may also be classified according to the technique used for their preparation, including:

- Melting or fusion method
- Solvent evaporation method
- Hot-melt extrusion
- Spray drying
- Co-precipitation

Each preparation method influences the physical characteristics, stability, dissolution behavior, and scalability of the formulation. Contemporary solid dispersion systems predominantly emphasize amorphous dispersions prepared using polymeric carriers due to their superior performance and suitability for industrial manufacturing [17–19].

4. Formulation Design and Selection Criteria

The formulation design of solid dispersions is a critical determinant of their solubility enhancement, dissolution performance, stability, and bioavailability. Development of a successful SD system requires systematic evaluation of drug properties, appropriate carrier selection, optimization of drug-to-carrier ratio, and careful choice of the processing technique [20–22].

4.1 Selection of Drug Candidates:

Drugs that are suitable for solid dispersion technology typically exhibit poor aqueous solubility and belong to BCS class II or IV. Key factors influencing drug suitability include: Thermal stability: The drug should be capable of tolerating processing temperatures, particularly when melt-based techniques are employed, without undergoing chemical degradation [23]. Molecular weight and crystallinity: Drugs with relatively low molecular weight and high crystallinity are more readily converted into an amorphous form, which contributes to enhanced dissolution behavior [8, 24]. Dose: Solid dispersion systems are generally more appropriate for drugs administered at low to moderate doses, as high-dose drugs may require excessive amounts of carrier material, increasing formulation bulk and complexity [25].

4.2 Selection of Carriers

Selection of Carriers play a fundamental role in enhancing solubility, stabilizing the amorphous drug form, and improving dissolution characteristics of solid dispersions. An ideal carrier should be hydrophilic, pharmaceutically acceptable, chemically inert, and capable of forming strong interactions with the drug molecule to prevent recrystallization [11, 26]. 6 Commonly employed carriers include: Polyethylene glycol (PEG): Enhances drug wettability and promotes rapid dissolution. Polyvinylpyrrolidone (PVP): Facilitates formation of stable amorphous dispersions through hydrogen bonding interactions. Hydroxypropyl methylcellulose (HPMC): Acts as a crystallization inhibitor and improves dissolution performance. Surfactants such as poloxamers: Improve wettability and contribute to enhanced solubilization of poorly soluble drugs [14, 27].

4.3 Drug-to-Carrier Ratio

The ratio of drug to carrier is a key formulation variable influencing both dissolution behavior and physical stability. Higher carrier content generally leads to improved dissolution and stabilization of the amorphous form; however, excessive carrier levels may increase formulation bulk, complicate processing, and raise manufacturing costs. Therefore, careful optimization is required to achieve an optimal balance between performance and practicality [6, 28].

4.4 Excipients and Additives

Additional excipients such as surfactants, stabilizers, plasticizers, and antioxidants may be incorporated into solid dispersion formulations to inhibit recrystallization, enhance wettability, and protect thermolabile drugs during processing and storage [16, 29].

4.5 Consideration of Processing Method

The choice of preparation technique-including melting, solvent evaporation, hot-melt extrusion, or spray drying-has a direct impact on drug dispersion, crystallinity, particle size, and scalability. Compatibility between the drug and carrier must be carefully evaluated in relation to the selected manufacturing process to ensure optimal performance and long-term stability of the solid dispersion system [15, 30]. A rational formulation strategy that integrates appropriate drug selection, carrier choice, excipient optimization, and processing method is essential to achieve enhanced solubility, improved dissolution, and consistent bioavailability in solid dispersion- based drug delivery systems.

5. Preparation Methods of Solid Dispersions

The method selected for the preparation of solid dispersions has a significant influence on their physicochemical characteristics, dissolution behavior, stability, and bioavailability. Selection of an appropriate technique depends on several factors, including the thermal stability of the drug, its solubility profile, compatibility with the carrier, and feasibility of scale-up for industrial production [31–33].

5.1 Melting (Fusion) Method

The melting or fusion method represents one of the earliest and most straightforward approaches for preparing solid dispersions. In this technique, the drug and carrier are heated together above their eutectic or melting temperature until a homogeneous molten mixture is obtained. The melt is then rapidly cooled, solidified, and subsequently milled and sieved to obtain a uniform powder [1, 2]. This method offers advantages such as simplicity, elimination of organic solvents, and cost-effectiveness. However, its application is restricted to drugs and carriers that are thermally stable and miscible in the molten state. Potential drawbacks include thermal degradation of heat- sensitive drugs and the risk of phase separation during cooling [6, 34].

5.2 Solvent Evaporation Method

In the solvent evaporation method, both the drug and carrier are dissolved in a common volatile solvent or solvent system. The solvent is then removed by evaporation under reduced pressure or controlled heating, resulting in the formation of a solid dispersion [11, 35]. This approach is particularly suitable for drugs that are sensitive to elevated temperatures. Despite its ability to achieve good molecular-level dispersion, the solvent evaporation method presents limitations related to residual solvent content, environmental and safety concerns, and challenges associated with complete solvent removal, especially during large-scale manufacturing [14, 36].

5.3 Hot-Melt Extrusion (HME)

Hot-melt extrusion is an advanced and widely used industrial technique for the production of solid dispersions. The process involves subjecting a physical mixture of drug and polymer to controlled heat and mechanical shear within an extruder, resulting in uniform molecular dispersion of the drug within the polymeric matrix [15, 37]. HME offers several advantages, including continuous processing, excellent content uniformity, scalability, and the absence of organic solvents. However, the relatively high processing temperatures and shear forces involved may limit its suitability for thermolabile or shear-sensitive drug substances [16, 38]. 8

5.4 Spray Drying

Spray drying is a commonly employed technique for preparing amorphous solid dispersions. In this method, the drug and carrier are dissolved or suspended in an appropriate solvent system and then atomized into a heated drying chamber. Rapid solvent evaporation results in the formation of fine, dry particles with high amorphous content [39, 40]. This technique allows precise control over particle size distribution and is particularly effective in enhancing dissolution behavior. Nevertheless, high operational costs, solvent handling requirements, and energy consumption may restrict its routine application in some manufacturing settings [41].

5.5 Co-precipitation Method

In the co-precipitation method, the drug and carrier are initially dissolved separately and then combined under controlled conditions to induce simultaneous precipitation. This technique enables uniform distribution of the drug within the carrier matrix and allows some degree of control over particle size and morphology [42].

5.6 Freeze Drying (Lyophilization)

Freeze drying involves freezing a solution containing both the drug and carrier, followed by sublimation of the solvent under reduced pressure. The resulting product is a highly porous solid dispersion, which facilitates rapid penetration of dissolution medium and enhanced dissolution rates [43, 44]. Although freeze drying is particularly useful for heat-sensitive drugs, the method is time-intensive, costly, and difficult to scale up, which limits its widespread industrial application.

6. Characterization of Solid Dispersions

Comprehensive characterization of solid dispersions is essential to confirm drug amorphization, evaluate drug–carrier interactions, assess physical stability, and predict in vitro and in vivo performance [45].

6.1 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry is widely used to evaluate the thermal properties of solid dispersions, including melting behavior, glass transition temperature, and degree of crystallinity. The disappearance or significant reduction of the drug's characteristic melting endotherm indicates successful conversion to an amorphous or molecularly dispersed state within the carrier matrix [6, 46].

6.2 Powder X-Ray Diffraction (PXRD)

Powder X-ray diffraction is a key analytical technique for assessing the crystalline or amorphous nature of solid dispersions. The absence of sharp diffraction peaks or a reduction in peak intensity suggests transformation of the crystalline drug into an amorphous form or its molecular dispersion within the carrier system [8, 47].

6.3 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is employed to investigate potential drug–carrier interactions, such as hydrogen bonding and other intermolecular forces. These interactions play a crucial role in stabilizing amorphous solid dispersions and preventing drug recrystallization during storage [11, 48].

6.4 Scanning Electron Microscopy (SEM)

Scanning electron microscopy provides detailed information on surface morphology, particle size, and shape of solid dispersion systems. Changes in surface characteristics compared to the pure drug and physical mixtures indicate successful dispersion of the drug within the carrier matrix [49].

6.5 In Vitro Dissolution Studies

In vitro dissolution testing is used to evaluate the release behavior of drugs from solid dispersions under simulated gastrointestinal conditions. A significantly enhanced dissolution rate compared to the pure drug or physical mixture confirms the effectiveness of the solid dispersion approach [50].

7. Mechanisms of Solubility and Bioavailability Enhancement

Solid dispersion technology improves solubility and oral bioavailability through a combination of interrelated physicochemical mechanisms. These mechanisms act collectively to enhance dissolution rate, facilitate gastrointestinal absorption, and ultimately improve the therapeutic performance of poorly water- soluble drugs [1, 6].

7.1 Reduction in Particle Size

In solid dispersion systems, the drug is dispersed at a molecular or near-molecular level within a hydrophilic carrier matrix. This results in a substantial reduction in the effective particle size of the drug, leading to a marked increase in surface area available for dissolution. According to the Noyes–Whitney equation, this increase in surface area directly contributes to an enhanced dissolution rate [2, 5].

7.2 Improved Wettability

Hydrophilic carriers used in solid dispersions significantly improve the wettability of drug particles. Enhanced wettability promotes rapid penetration of the dissolution medium into the solid matrix and reduces interfacial tension between the drug and the aqueous environment, thereby facilitating faster dissolution and improved drug release [11, 26].

7.3 Conversion to Amorphous State

A major advantage of solid dispersion technology is the stabilization of drugs in an amorphous form. Amorphous drugs possess higher free energy and greater molecular mobility compared to their crystalline counterparts. This thermodynamically less stable state results in increased apparent solubility and accelerated dissolution rates [8, 10, 46].

7.4 Formation of Solid Solutions

In solid solution systems, drug molecules are uniformly dispersed at the molecular level within the carrier lattice. This homogeneous distribution eliminates crystalline boundaries and reduces energy barriers for dissolution, leading to rapid drug release and enhanced bioavailability [6, 7].

7.5 Prevention of Drug Aggregation

Solid dispersions inhibit aggregation and agglomeration of drug particles during the dissolution process. The carrier matrix maintains physical separation between drug molecules, preventing the formation of large aggregates and ensuring consistent and reproducible dissolution behavior [14, 27].

7.6 Maintenance of Supersaturation

Certain polymers and surfactants used in solid dispersions act as crystallization inhibitors in the gastrointestinal environment. These excipients help maintain a supersaturated drug state for an extended period, thereby enhancing the concentration gradient across the intestinal membrane and improving oral bioavailability [15, 16].

8. Pharmaceutical Applications of Solid Dispersions

Solid dispersion technology has been widely applied in the formulation of poorly soluble drugs to improve solubility, dissolution rate, and oral bioavailability across various therapeutic classes [17, 19].

8.1 Enhancement of Oral Bioavailability

Numerous preclinical and clinical studies have demonstrated significant enhancement in the oral bioavailability of BCS class II drugs formulated as solid dispersions. Improved dissolution behavior leads to higher plasma drug concentrations and enhanced therapeutic efficacy [20, 22].

8.2 Immediate-Release Formulations

Solid dispersions are extensively utilized in immediate-release dosage forms to achieve rapid drug release and faster onset of therapeutic action. This approach is particularly beneficial for drugs that require prompt pharmacological effects [28, 50].

8.3 Controlled and Sustained Release Systems

By appropriate selection of polymers and optimization of drug-to-carrier ratios, solid dispersions can be designed to provide controlled or sustained drug release profiles while still maintaining enhanced solubility and dissolution characteristics [30, 37].

8.4 Fixed-Dose Combinations

Solid dispersion technology supports the development of fixed-dose combination products containing poorly soluble drugs. Improved compatibility and synchronized dissolution behavior of multiple active pharmaceutical ingredients can be achieved through this approach [25, 39].

8.5 Commercial Products

Several marketed pharmaceutical products employ solid dispersion technology, highlighting its industrial feasibility and regulatory acceptance. These formulations demonstrate improved bioavailability, reduced variability in drug absorption, and enhanced patient compliance [17–19].

9. Stability and Regulatory Considerations

Physical and chemical stability are among the most critical challenges associated with the development of solid dispersion systems, particularly those containing drugs in an amorphous state [45]. Stability issues must be carefully addressed to ensure consistent performance, safety, and therapeutic efficacy throughout the product's shelf life.

9.1 Physical Stability

Amorphous solid dispersions are thermodynamically unstable and exhibit a natural tendency to recrystallize over time. Recrystallization may result in reduced solubility and compromised dissolution performance. Selection of appropriate polymeric carriers, optimization of drug– carrier interactions, and control of processing and storage conditions are essential strategies to enhance physical stability. In addition, suitable packaging systems that limit exposure to moisture and temperature fluctuations play a crucial role in maintaining long-term stability [46– 48].

9.2 Chemical Stability

Chemical degradation of drugs within solid dispersions may occur due to exposure to environmental factors such as moisture, heat, light, and oxygen. Incorporation of stabilizing excipients and antioxidants, along with adherence to optimized manufacturing conditions, can minimize degradation. Comprehensive stability studies conducted in accordance with International Council for Harmonisation

(ICH) guidelines are mandatory to establish shelf life and appropriate storage conditions [29, 31].

9.3 Regulatory Aspects

From a regulatory perspective, solid dispersion-based products require extensive physicochemical characterization, stability data, and demonstration of consistent in vitro performance. Regulatory authorities also emphasize the establishment of in vitro–in vivo correlations where applicable. Advances in analytical methodologies and increased regulatory familiarity with amorphous solid dispersions have contributed to improved acceptance of these systems for commercial pharmaceutical products [18, 21].

10. Scale-Up and Industrial Manufacturing Considerations

Successful translation of solid dispersion technology from laboratory scale to commercial manufacturing requires careful consideration of process scalability, reproducibility, product stability, and regulatory compliance. Scale-up challenges often arise due to variations in heat transfer, mixing efficiency, solvent removal, and batch-to-batch uniformity [31–33]. Among available techniques, hot-melt extrusion and spray drying are the most widely adopted for industrial-scale production of solid dispersions. Hot-melt extrusion enables continuous processing and precise control over critical process parameters such as temperature, screw speed, and residence time, resulting in uniform drug dispersion and consistent product quality [15, 37]. Spray drying offers excellent control over particle size distribution and amorphous content, making it particularly suitable for largescale manufacturing of amorphous solid dispersions [39– 41]. Optimization of critical processing parameters is essential to prevent thermal degradation, phase separation, and recrystallization during manufacturing. Furthermore, downstream processing steps, 13 including milling, blending, and compression, must be carefully managed to preserve the physicochemical integrity and dissolution performance of solid dispersions in the final dosage form [30, 38].

11. Recent Advances and Future Trends

Recent research in solid dispersion technology has focused on improving physical stability, prolonging supersaturation, and enhancing in vivo drug performance. Development of novel polymers, polymer blends, and polymer–surfactant systems has shown promise in inhibiting drug crystallization and maintaining long-term stability of amorphous solid dispersions [14–16]. Emerging strategies include the use of bio-relevant polymers, pH-responsive carriers, and nanostructured solid dispersions to achieve targeted drug release and improved absorption profiles. In addition, computational tools and molecular modeling techniques are increasingly being applied to predict drug– polymer miscibility and guide rational formulation development [20, 22, 26, 48]. The integration of solid dispersion technology with continuous manufacturing platforms and quality-by design (QbD) principles is expected to further enhance product quality, process robustness, and regulatory confidence. These advancements are likely to expand the application of solid dispersions in the development of next-generation oral drug delivery systems [18, 21].

12. Conclusion

Solid dispersion technology represents a robust and versatile approach for improving the solubility and oral bioavailability of poorly water-soluble drugs, particularly those classified under BCS class II and IV. By incorporating drugs into hydrophilic carriers or polymeric matrices, solid dispersions enhance wettability, reduce crystallinity, accelerate dissolution, and promote gastrointestinal absorption. Continuous advancements in formulation strategies, preparation methods, and characterization techniques have significantly improved the stability and industrial feasibility of solid dispersion systems. Although challenges related to physical stability and large-scale manufacturing persist, ongoing innovation in carrier materials, processing technologies, and regulatory science continues to strengthen the role of solid dispersions in pharmaceutical development. Solid dispersion technology is expected to remain a cornerstone strategy for overcoming solubility-related limitations and improving therapeutic outcomes of orally administered drugs.

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