JETIR.ORG | ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Solid Dispersion Techniques for Solubility Enhancement: A Comprehensive Review

Chandra Prakash Maurya[1], Mr. Sagar Bansal*, Mrs. Rajbala Singh[2], Dr. Arvind kumar Srivastava[3].

Research scholar[1], Associate professor*, Assistant professor[2], Professor and Director[3]

***Corresponding Author: Mr. Sagar Bansal**

Shambhunath Institute of Pharmacy, Jhalwa Pryagraj U.P

Abstract

Poor aqueous solubility remains one of the most significant challenges in modern drug development, limiting the bioavailability and therapeutic effectiveness of many promising drug candidates. Solid dispersion is a formulation strategy designed to address this issue by dispersing poorly water-soluble drugs in an inert carrier matrix, thereby enhancing their dissolution rate and solubility. This review aims to provide a comprehensive discussion on solid dispersion technology, covering the various preparation techniques, underlying mechanisms of solubility enhancement, types of carriers employed, and the advantages offered by this approach, such as improved bioavailability and dose reduction. Additionally, it examines key limitations, including physical instability and scale-up challenges, while also exploring future prospects and emerging trends in the field that hold promise for overcoming these barriers and advancing pharmaceutical development.

Keywords

Solid dispersion, solubility enhancement, amorphous systems, pharmaceutical technology, drug delivery

1. Introduction

Problem of Poor Solubility

Poor aqueous solubility is widely recognized as one of the most critical barriers in oral drug delivery. Approximately 40% of currently marketed drugs and an even higher proportion—around 90% of new chemical entities (NCEs)—exhibit poor water solubility (Lipinski, 2000; Savjani et al., 2012). This poor solubility translates directly to low and variable oral bioavailability, limiting the therapeutic efficacy of otherwise potent drug candidates. Drugs with insufficient solubility often fail to achieve adequate plasma concentrations, necessitating higher doses that can increase the risk of adverse effects and reduce patient compliance. In the context of the Biopharmaceutics Classification System (BCS), classes II and IV compounds, which have low solubility, represent significant formulation challenges in the pharmaceutical industry.(1,2)

Solid dispersion refers to the molecular or particulate dispersion of poorly water-soluble drugs within an inert, typically hydrophilic carrier matrix. In this system, the drug is molecularly dispersed, amorphous, or finely crystalline within the carrier, leading to improved wettability, reduced particle size, and often conversion to a high-energy amorphous form. These physicochemical changes collectively enhance the dissolution rate and apparent solubility of the drug, facilitating improved bioavailability after oral administration. (3)

The concept of solid dispersion was first introduced by Sekiguchi and Obi in 1961, who demonstrated that dispersing sulfonamides in a water-soluble carrier such as urea could substantially improve their dissolution rate

(Sekiguchi & Obi, 1961). This pioneering work laid the foundation for decades of research and development into solid dispersion systems, which remain a vital strategy in contemporary pharmaceutical formulation. (4)

2. Classification of Solid Dispersions

Solid dispersions (SDs) can be classified in multiple ways depending on their composition, preparation method, and internal structure. Two commonly used classification systems are (1) by generation, reflecting technological evolution, and (2) by molecular arrangement, describing the physical state and distribution of the drug in the carrier.

1. Classification by Generation

First Generation: Crystalline drug in crystalline carriers

- These are the earliest solid dispersions, typically eutectic systems where both the drug and carrier remain crystalline.
- Dissolution enhancement is achieved primarily through particle size reduction and improved wetting.
- Examples: Sulfathiazole-urea eutectic mixtures as introduced by Sekiguchi and Obi (1961).
- Limitation: Limited solubility enhancement compared to amorphous systems, tendency for phase separation.

Second Generation: Amorphous drug in polymeric carriers

- The drug is molecularly dispersed in an amorphous state within hydrophilic polymers (e.g., PVP, HPMC, PEG).
- Dissolution rate increases due to improved wettability, lack of crystalline lattice energy, and molecular-level dispersion.
- More stable than first-generation systems if properly formulated, but may suffer from physical instability due to recrystallization over time.
- Examples: Itraconazole–HPMC solid dispersions.

Third Generation: Use of surfactants/polymer combinations

- Combines polymers with surfactants to further enhance solubility, wettability, and physical stability.
- Surfactants help prevent drug recrystallization and improve dispersion during dissolution.
- Examples of surfactants: Poloxamers, Tween, Soluplus®.
- This generation addresses some of the stability challenges of second-generation systems.

Fourth Generation: Controlled release solid dispersions

- Designed to not only improve solubility but also provide controlled or sustained drug release.
- Utilizes polymers with specific release-modifying properties, allowing tailoring of the dissolution profile.
- Applications include chronotherapy and targeted delivery systems.
- Examples: Hydrophilic and hydrophobic polymer combinations that modulate release kinetics.

2.1.Classification by Molecular Arrangement

Eutectic mixtures

- Physical mixtures of crystalline drug and carrier that melt and solidify as intimate crystalline aggregates at a eutectic composition.

- Characterized by simultaneous crystallization of both components.
- Improved dissolution via reduced particle size and improved wettability.
- Example: Sulfathiazole–urea eutectic.

Solid solutions

- Drug molecules molecularly dispersed in the carrier matrix.
- Two types:
    - Continuous solid solutions: Complete miscibility of drug and carrier at molecular level across all compositions. Rare in pharmaceuticals.
    - Discontinuous solid solutions: Partial miscibility; drug dissolves in carrier up to a certain limit.
- Provides high thermodynamic stability of the amorphous state.

Glass solutions

- Single-phase amorphous systems where the drug is molecularly dissolved in an amorphous carrier matrix.
- Thermodynamically metastable but kinetically stable if well formulated.
- Dissolution rate is significantly improved due to lack of crystalline lattice.
- Examples: Indomethacin–PVP systems.

Glass suspensions

- Amorphous carrier matrix in which the drug exists as dispersed amorphous or microcrystalline particles.
- The carrier stabilizes the high-energy amorphous form of the drug.
- Intermediate dissolution behavior between eutectic mixtures and glass solutions. (5-10)

Table title: *Classification of Solid Dispersions by Generation and Molecular Arrangement*

Generation	**Features**	**Examples**
First Generation	Crystalline drug + crystalline carrier	Sulfathiazole–urea systems
Second Generation	Amorphous drug + polymeric carrier	PVP, HPMC dispersions
Third Generation	Polymers + surfactants	Soluplus®, Poloxamer combinations
Fourth Generation	Controlled-release systems	Coated or matrix-based dispersions

3. Mechanisms of Solubility Enhancement

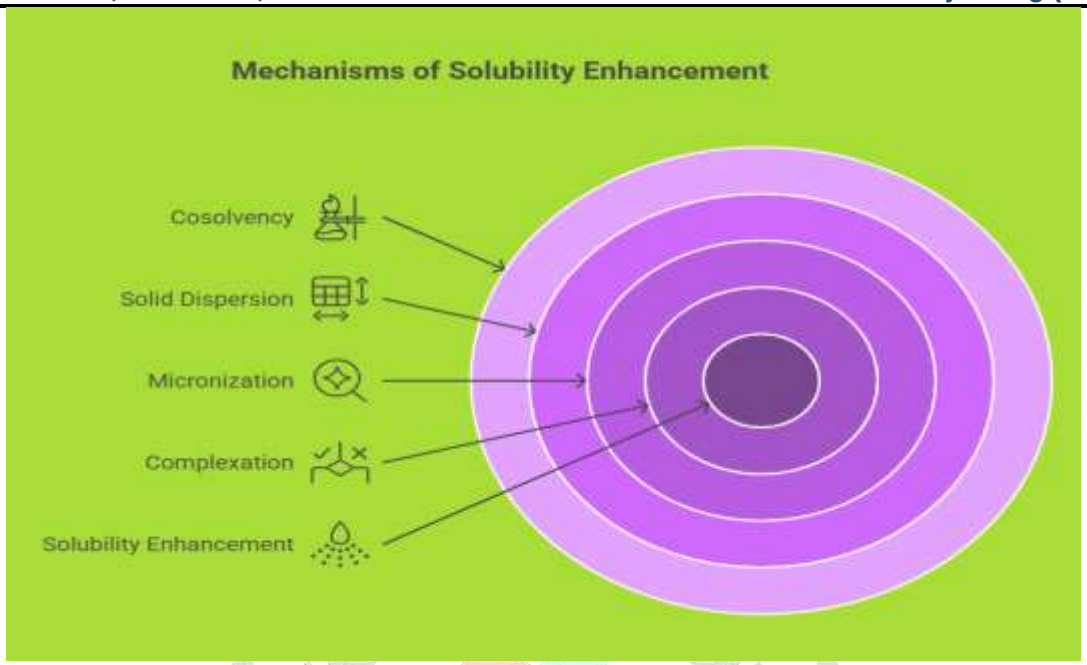

Figure 1: Mechanisms of Solubility Enhancement

Solid dispersions improve the solubility and dissolution rate of poorly water-soluble drugs through multiple interrelated mechanisms. First, reduction of drug particle size to the molecular or near-molecular level dramatically increases the effective surface area available for dissolution, thereby enhancing the dissolution rate in accordance with the Noyes–Whitney equation (Chiou & Riegelman, 1971). Second, hydrophilic carriers in solid dispersions significantly improve the wettability of the drug particles; polymers such as polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) reduce interfacial tension between drug and dissolution medium, promoting faster wetting and dispersion (Leuner & Dressman, 2000). Third, drugs in solid dispersions often exist in an amorphous form, which possesses higher Gibbs free energy compared to the crystalline state. This increased thermodynamic activity translates to enhanced apparent solubility and faster dissolution rates, as the energy barrier for dissolution is lower (Vasconcelos et al., 2007). Fourth, polymers and surfactants used in these formulations help prevent recrystallization by forming hydrogen bonds or other interactions with the drug, stabilizing it in its amorphous state and maintaining its solubility advantage over time. Finally, solid dispersions promote improved dispersibility in aqueous media, enabling the formation of fine colloidal or molecular dispersions upon contact with gastrointestinal fluids, ensuring uniform and rapid drug release for absorption. Collectively, these mechanisms make solid dispersions one of the most versatile and effective strategies for enhancing the bioavailability of poorly water-soluble drugs. (11-13)

Table 2: Common Carriers Used in Solid Dispersions

Carrier Type	Examples	Properties / Advantages
Hydrophilic polymers	PVP, HPMC, PEG	Improved wettability, solubility
Surfactants	Poloxamer, Tween	Reduced interfacial tension
Sugars/sugar alcohols	Mannitol, Lactose	Cost-effective, safe
Novel carriers	Soluplus®, Cyclodextrins	Controlled release, complexation

4. Carriers Used in Solid Dispersions

The choice of carrier is critical in the design of solid dispersions, as it governs the solubility enhancement, physical stability, and manufacturability of the final formulation. Hydrophilic polymers are the most commonly employed carriers due to their excellent solubilizing and stabilizing properties. *Polyvinylpyrrolidone (PVP)* is widely used because of its high water solubility, ability to form hydrogen bonds with drugs, and capacity to stabilize the amorphous state, thereby preventing recrystallization (Leuner & Dressman, 2000). *Hydroxypropyl*

methylcellulose (HPMC) is another widely used polymer, valued for its gel-forming ability in aqueous media, which enhances wettability and provides sustained stabilization of amorphous drug forms (Vasconcelos et al., 2007). *Polyethylene glycol (PEG)*, a low-molecular-weight hydrophilic polymer, acts as both a carrier and plasticizer, lowering the melting temperature during melt-based preparation methods while enhancing drug wettability and dissolution rate (Craig, 2002).

Surfactants are often included in solid dispersions to further enhance solubility and prevent recrystallization. *Poloxamers*, which are amphiphilic block copolymers, improve wettability, lower interfacial tension, and can form micelles that solubilize poorly soluble drugs (Vasconcelos et al., 2007). *Tween* (e.g., Tween 80) is a non-ionic surfactant frequently used to enhance drug dispersion and maintain supersaturation during dissolution, reducing the risk of precipitation.

Sugars and sugar alcohols such as *mannitol* and *lactose* are employed as carriers in some systems, particularly in spray-dried dispersions, due to their hydrophilicity, biocompatibility, and ability to improve wettability and dissolution rates (Serajuddin, 1999).

Novel carriers have emerged to address the limitations of traditional systems. *Cyclodextrins* are cyclic oligosaccharides capable of forming inclusion complexes with hydrophobic drugs, thereby enhancing aqueous solubility and stabilizing amorphous forms (Loftsson & Duchêne, 2007). *Soluplus*® is an amphiphilic graft copolymer specifically designed for solid dispersion technology; it combines hydrophilic and lipophilic segments to improve drug wettability, maintain supersaturation, and inhibit recrystallization, offering superior performance over traditional polymers for many poorly soluble drugs (Blattner et al., 2014).

Together, these carriers provide formulators with a wide toolbox to tailor solid dispersion systems for specific drugs, balancing solubility enhancement, stability, and manufacturability to achieve optimal therapeutic outcomes. (14-19)

5. Preparation Techniques for Solid Dispersions

Solid dispersions can be prepared using various techniques, each with distinct advantages and limitations tailored to the physicochemical properties of the drug and carrier. Fusion (melting) method is one of the simplest approaches, in which the drug and hydrophilic carrier are heated until melted together, followed by controlled cooling to yield a solidified dispersion. This method is solvent-free and straightforward but is limited by the risk of thermal degradation for heat-sensitive drugs (Sekiguchi & Obi, 1961; Craig, 2002). Solvent evaporation method involves dissolving both drug and carrier in a common volatile solvent, then removing the solvent under reduced pressure or ambient conditions to form a molecularly dispersed solid. This technique allows processing at lower temperatures, making it suitable for thermolabile compounds, but concerns over solvent toxicity and residual solvent levels remain important regulatory challenges (Leuner & Dressman, 2000).

Table 3: Advantages and Limitations of Each Technique

Technique	Advantages	Limitations
Fusion method	Simple, solvent-free	Thermal degradation
Solvent evaporation	Low temperature	Solvent residues, toxicity
Hot-melt extrusion	Continuous, scalable	Expensive equipment, heat sensitivity
Spray drying	Scalable, rapid	Solvent handling
Supercritical fluid	Low residue	Costly equipment
Cryogenic methods	Low temperature	Expensive, time-consuming
Microwave irradiation	Energy-efficient	Scale-up challenges

Hot-melt extrusion (HME) has emerged as an advanced, continuous, and scalable method that combines heat and mechanical shear to intimately mix drug and polymer, producing uniform solid dispersions. HME avoids the use of solvents and enables precise control over process parameters, but requires significant initial investment and may still pose challenges for highly thermosensitive drugs (Maniruzzaman et al., 2012). Spray drying involves atomizing a drug–polymer solution into a stream of hot air, causing rapid solvent evaporation and formation of fine amorphous particles. It offers high scalability and precise control over particle morphology, although careful management of solvent handling and potential environmental impact is required (Vasconcelos et al., 2007).

Supercritical fluid techniques, particularly using supercritical carbon dioxide, provide an alternative solvent-free approach where the drug and carrier are either dissolved or precipitated under mild conditions. These methods yield dispersions with low residual solvents and controlled particle properties, but require specialized, expensive equipment (York, 1999). Cryogenic methods such as spray freezing or freeze-drying involve rapid freezing of the drug–carrier solution followed by lyophilization, enabling processing at extremely low temperatures suitable for heat-sensitive compounds, although these techniques are relatively complex and costly (Mishra et al., 2006). Finally, microwave irradiation offers energy-efficient localized heating to melt and disperse drug–polymer mixtures, providing rapid processing with reduced energy consumption; however, challenges remain in scaling up this technology for industrial production due to non-uniform heating and equipment limitations (Patel et al., 2015). Overall, the choice of preparation technique depends on the drug's thermal stability, solvent compatibility, target product properties, and manufacturing scale, with ongoing research aiming to optimize these methods for improved efficiency and product performance. (20-27)

6. Characterization of Solid Dispersions

Comprehensive characterization of solid dispersions is essential to ensure successful formulation development, confirm physical states, and predict in vivo performance. Differential Scanning Calorimetry (DSC) is widely used to assess the amorphous or crystalline state of the drug within the carrier matrix by measuring thermal transitions such as melting points or glass transition temperatures. The disappearance or broadening of the drug's melting endotherm in DSC thermograms typically indicates amorphous dispersion or molecular-level mixing (Craig, 2002). Powder X-ray Diffraction (PXRD) provides complementary evidence of crystallinity by detecting sharp diffraction peaks characteristic of crystalline materials; the absence or reduction of these peaks in solid dispersions confirms amorphization (Leuner & Dressman, 2000).

Fourier Transform Infrared Spectroscopy (FTIR) is employed to investigate potential drug–carrier interactions such as hydrogen bonding or ionic interactions, which can stabilize the amorphous form and inhibit recrystallization. Shifts in characteristic absorption bands often indicate specific intermolecular interactions (Vasconcelos et al., 2007). Scanning Electron Microscopy (SEM) enables visualization of surface morphology and particle size, offering insights into the homogeneity and dispersion of the drug within the carrier matrix. Changes in surface texture and morphology after processing can also reveal successful amorphization and improved wettability (Serajuddin, 1999).

Finally, dissolution testing remains a critical in vitro method for evaluating the performance of solid dispersions, directly measuring improvements in dissolution rate and extent relative to crystalline or physical mixtures of the drug. Enhanced dissolution profiles typically predict improved bioavailability for poorly water-soluble drugs, making dissolution testing a key quality control and formulation optimization tool (Vasconcelos et al., 2007). By combining these complementary analytical techniques, formulators can thoroughly evaluate the physicochemical properties, stability, and performance of solid dispersions, guiding rational design for effective oral delivery of poorly soluble drugs. (28-31)

7. Advantages of Solid Dispersion Techniques

Solid dispersion technology offers several key advantages in overcoming poor aqueous solubility of drugs. Primarily, it significantly enhances dissolution rate and oral bioavailability by converting drugs into amorphous or molecularly dispersed forms with higher Gibbs free energy and improved wettability (Leuner & Dressman, 2000). This improvement can lead to reduced dose variability and more predictable pharmacokinetics, crucial for

ensuring consistent therapeutic outcomes, especially for BCS Class II drugs. Additionally, reformulating existing drugs into solid dispersions can support patent life extension strategies by offering novel formulations with superior performance. In some systems, particularly those with strong drug–polymer interactions, solid dispersions can even improve stability by inhibiting recrystallization during storage (32-33).

Table 4: Characterization Techniques for Solid Dispersions

Technique	Purpose	Example Result/Observation
DSC	Detect melting point / amorphous state	Shift in endothermic peak
PXRD	Crystallinity	Disappearance of sharp peaks
FTIR	Drug-carrier interaction	Shift in characteristic peaks
SEM	Morphology	Surface texture changes
Dissolution test	In vitro performance	Faster dissolution rate

8. Limitations and Challenges

Despite these benefits, solid dispersions face notable challenges. Physical instability is a major concern, as the high-energy amorphous form tends to recrystallize over time, potentially reducing solubility advantages. Many polymers are also moisture-sensitive, with absorbed water acting as a plasticizer that promotes recrystallization or phase separation. From an industrial perspective, scale-up and manufacturing complexity pose practical hurdles; techniques like spray drying or hot-melt extrusion require precise control and specialized equipment. Regulatory requirements add another layer of challenge, especially regarding residual solvent limits as governed by ICH guidelines (e.g., ICH Q3C), necessitating rigorous solvent removal and testing to ensure patient safety (34).

9. Recent Advances and Trends

To address these challenges, recent research has focused on innovative solutions. Co-amorphous systems—where two drugs or a drug and an excipient stabilize each other in an amorphous matrix—offer improved physical stability without polymers (Chieng et al., 2013). The use of novel polymers and surfactants, such as Soluplus® or copovidone, improves miscibility and prevents recrystallization. Cutting-edge technologies like 3D printing of solid dispersions enable precise control over dose and geometry, opening avenues for personalized medicine. Molecular modeling and predictive tools are increasingly employed to screen excipients and design optimal formulations in silico, reducing experimental burden and improving formulation success rates (35).

Table 5: Marketed Solid Dispersion Products

Product Name	Drug	Carrier/Technique	Company
Kaletra®	Lopinavir/Ritonavir	Melt extrusion	Abbott
Sporanox®	Itraconazole	Spray drying with polymers	Janssen
Rezulin®	Troglitazone	Melt extrusion	Parke-Davis

10. Regulatory and Industrial Perspectives

Regulatory authorities emphasize controlling residual solvents per ICH Q3C guidelines, necessitating validated solvent evaporation and testing processes. Stability testing requirements ensure long-term performance by assessing physical and chemical stability under defined storage conditions (ICH Q1A). The Quality by Design (QbD) paradigm encourages systematic formulation development, defining critical quality attributes (CQAs) and process parameters to ensure consistent product quality. Importantly, solid dispersion technology has demonstrated industrial success, with marketed products such as Kaletra® (lopinavir/ritonavir) melt-extruded dispersions and Sporanox® (itraconazole) spray-dried dispersions validating the commercial feasibility and therapeutic benefits of this approach (36).

11. Future Prospects

Looking ahead, the field is moving toward personalized solid dispersions, where patient-specific doses and release profiles can be manufactured via technologies like 3D printing. Emphasis on green manufacturing methods aims to reduce or eliminate solvents, minimizing environmental impact and regulatory hurdles. Integration with nanotechnology promises further improvements in bioavailability by enabling nanoparticle or nanofiber dispersions. Finally, advances in in silico design and molecular modeling will continue to streamline formulation development, predicting drug–carrier compatibility and stability with greater accuracy, reducing development time and cost while improving success rates for challenging poorly soluble drugs. (37)

Table 6: Future Research Directions

Area	Description	Potential Benefit
Personalized medicine	Patient-specific formulations	Better efficacy, safety
Green manufacturing	Solvent-free/eco-friendly methods	Regulatory, environmental compliance
Co-amorphous systems	Drug–drug/excipient stabilization	Improved stability
Predictive modeling	In silico screening of carriers	Faster development cycle

12. Conclusion

Solid dispersions remain one of the most effective and versatile formulation strategies for overcoming the pervasive problem of poor aqueous solubility, which limits the bioavailability of many new chemical entities. By converting poorly soluble drugs into amorphous or molecularly dispersed forms within hydrophilic carriers, solid dispersions can dramatically enhance dissolution rates and oral absorption (Leuner & Dressman, 2000; Vasconcelos et al., 2007). However, realizing these benefits in commercial products requires careful consideration of the **c**hoice of preparation method**,** carrier selection**,** andscale-up strategyto ensure physical stability, reproducibility, and regulatory compliance. For example, techniques such as hot-melt extrusion and spray drying have been widely adopted in industry due to their scalability and ability to produce consistent, high-quality dispersions (Repka et al., 2007). Meanwhile, the selection of appropriate polymers, surfactants, or novel carriers like Soluplus® or cyclodextrins is essential for stabilizing the amorphous form and preventing recrystallization over shelf life (Craig, 2002). Looking forward, continuous innovation—including co-amorphous systems, advanced polymers, 3D printing, and predictive molecular modeling—is driving the development of more robust, patient-tailored, and environmentally sustainable formulations. These advances promise to further expand the applicability of solid dispersions, enabling the delivery of challenging drug molecules with improved safety, efficacy, and patient adherence in the pharmaceutical market.

References:

1. Lipinski, C. A. (2000). Drug-like properties and the causes of poor solubility and poor permeability. *Journal of Pharmacological and Toxicological Methods*, 44(1), 235–249.
2. Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: Importance and enhancement techniques. *ISRN Pharmaceutics*, 2012, 195727.
3. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today*, 12(23–24), 1068–1075.
4. Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulfathiazole and that of ordinary sulfathiazole in man. *Chemical & Pharmaceutical Bulletin*, 9(11), 866–872.
5. Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulfathiazole and that of ordinary sulfathiazole in man. *Chemical & Pharmaceutical Bulletin*, 9(11), 866–872.
6. Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. *Journal of Pharmaceutical Sciences*, 60(9), 1281–1302.
7. Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.
8. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today*, 12(23–24), 1068–1075.
9. Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
10. Vasconcelos, T., Marques, S., das Neves, J., & Sarmento, B. (2016). Amorphous solid dispersions: Rational selection of a manufacturing process. *Advanced Drug Delivery Reviews*, 100, 85–101.
11. Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. *Journal of Pharmaceutical Sciences*, 60(9), 1281–1302.
12. Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.
13. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today*, 12(23–24), 1068–1075.
14. Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.

15. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today*, 12(23–24), 1068–1075.
16. Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
17. Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *Journal of Pharmaceutical Sciences*, 88(10), 1058–1066.
18. Loftsson, T., & Duchêne, D. (2007). Cyclodextrins and their pharmaceutical applications. *International Journal of Pharmaceutics*, 329(1–2), 1–11.
19. Blattner, S., Rieck, W., Dresel, N., & Langguth, P. (2014). Soluplus®—a novel solubilizer for solid dispersions. *Journal of Excipients and Food Chemicals*, 5(1), 23–29.
20. Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulfathiazole and that of ordinary sulfathiazole in man. *Chemical & Pharmaceutical Bulletin*, 9(11), 866–872.
21. Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
22. Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.
23. Maniruzzaman, M., Boateng, J. S., Snowden, M. J., & Douroumis, D. (2012). A review of hot-melt extrusion: Process technology to pharmaceutical products. *ISRN Pharmaceutics*, 2012, 436763.
24. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today*, 12(23–24), 1068–1075.
25. York, P. (1999). Strategies for particle design using supercritical fluid technologies. *Pharmaceutical Science & Technology Today*, 2(11), 430–440.
26. Mishra, B., Patel, B. B., & Tiwari, S. (2006). Colloidal drug delivery system: A review. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 1(1), 267–284.
27. Patel, D. J., Patel, M. M., & Patel, K. N. (2015). Microwave technology: A novel approach for solid dispersion preparation. *Asian Journal of Pharmaceutics*, 9(3), 157–164.
28. Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
29. Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.
30. Vasconcelos, T., Sarmento, B., & Costa, P. (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today*, 12(23–24), 1068–1075.
31. Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *Journal of Pharmaceutical Sciences*, 88(10), 1058–1066.
32. Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 50(1), 47–60.
33. Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
34. Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *Journal of Pharmaceutical Sciences*, 88(10), 1058–1066.
35. Chieng, N., Aaltonen, J., Saville, D., & Rades, T. (2013). Physical characterization and stability of amorphous simvastatin–lysine solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 85(3), 878–886.
36. Vasconcelos, T., Marques, S., das Neves, J., & Sarmento, B. (2016). Amorphous solid dispersions: Rational selection of a manufacturing process. *Advanced Drug Delivery Reviews*, 100, 85–101.
37. Repka, M. A., Majumdar, S., Battu, S. K., McGinity, J. W., & Moolchandani, V. (2007). Applications of hot-melt extrusion for drug delivery. *Expert Opinion on Drug Delivery*, 4(5), 593–602.