Indonesian Journal of Pharmaceutics
IdJP
ISSN : 2597-8748

Vol. 7, Issue 2, 2025 (87-112)
http://journal.unpad.ac.id/IdJP

Ternary Solid Dispersions for Improved Dissolution Profile of Poorly Water-Soluble Drugs: Insights from Recent Studies

Salma Amaliah[1], Diah Lia Aulifa[2], Arif Budiman[*1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km. 21, Bandung 45363, Indonesia;
[2]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km. 21, Bandung 45363, Indonesia;

Submitted: 22/03/2025, Revised: 12/4/2025, Accepted: 15/05/2025, Published: 30/05/2025

ABSTRACT

Enhancing the dissolution of poorly water-soluble drugs remains a major challenge in drug development. Binary solid dispersions (BSDs), composed of a drug and a hydrophilic polymer, have been employed to improve solubility primarily through amorphization. However, many BSD systems suffer from limited wettability and suboptimal dispersion, which reduce their effectiveness in promoting rapid and consistent drug release. Ternary solid dispersions (TSDs) introduce a functional third component, such as an additional polymer, surfactant, co-former, or other excipient, to overcome these limitations and further enhance dissolution performance. This review provides a concise summary of current advancements in TSD systems and their underlying mechanisms for improving drug dissolution. Relevant studies published between 2020 and 2025 were retrieved from Scopus, Google Scholar, and PubMed using the keywords "ternary solid dispersion" and "dissolution." Critical formulation strategies, excipient combinations, and manufacturing techniques were summarized to elucidate how TSDs improve dissolution by stabilizing the amorphous state, inhibiting nucleation and crystal growth, enhancing wettability, and preventing particle agglomeration. The selected preparation method was determined to significantly affect dissolution behavior. The compiled evidence supports TSD systems as a versatile and efficient strategy for improving the dissolution characteristics of poorly water-soluble drugs, offering substantial potential for advancing oral drug delivery.

Keywords: Poorly water-soluble drug; amorphization; ternary solid dispersion; dissolution; drug release.

*Corresponding author,
e-mail: arif.budiman@unpad.ac.id A. Budiman)

https://doi.org/10.24198/idjp.v7i2.63625

1. Introduction

The formulation of oral pharmaceuticals for poorly water-soluble drugs remains a significant challenge in drug discovery. Aqueous solubility is essential for drug dissolution and bioavailability, especially for hydrophobic drugs [1,2]. An estimated 70–90% of new chemical entities in the current drug candidates under development exhibit limited aqueous solubility [3], particularly those categorized under the Biopharmaceutics Classification System (BCS) Class II and IV [1,4]. These compounds have low solubility and/or low permeability, resulting in inadequate dissolution in gastrointestinal fluids, which consequently leads to inconsistent absorption and diminished oral bioavailability. This persistent limitation has established solubility enhancement as a critical focus in modern drug formulation development [5]. For instance, drugs such as simvastatin, ritonavir, itraconazole, fenofibrate, and curcumin are known to have poor solubility, and often require advanced formulation strategies to achieve therapeutic plasma concentrations [6–10].

Nevertheless, many hydrophobic drug candidates continue to exhibit poor dissolution behavior, which significantly hinders their absorption and therapeutic performance. In oral drug delivery, when dissolution is the rate-limiting step for absorption, low solubility often results in suboptimal bioavailability and therapeutic failure, regardless of the compound's pharmacological activity [11,12]. Clinical practitioners commonly address this issue by increasing the dosage, but this approach introduces additional complications such as side effects, elevated treatment costs, and diminished patient compliance [13]. Therefore, improving dissolution performance is not only a formulation objective but also a critical factor in ensuring therapeutic efficacy.

Converting poorly soluble drugs from the crystalline state to the amorphous state is among the most effective strategies to enhance dissolution performance [14,15]. Amorphous drugs exhibit higher apparent solubility and accelerated dissolving rates compared to their crystalline form, primarily due to the absence of long-range molecular order and reduction in lattice energy [16,17]. Nonetheless, despite these advantages, amorphous drugs are thermodynamically unstable and highly susceptible to recrystallization during storage or dissolution, which may potentially compromise their therapeutic effectiveness [15,18].

To address this limitation, amorphous solid dispersion (ASD) systems have been extensively utilized to generate and stabilize the amorphous form. In ASDs, the drug is molecularly dispersed within a hydrophilic polymer matrix, which enhances wettability, inhibits recrystallization, and improves dissolution performance [19–22]. However, in some ASD systems, particularly binary solid dispersions (BSDs) composed of only a drug and a single polymer, inadequate improvement in wettability leads to additional challenges, including low drug loading capacity, physical instability, and suboptimal inhibition of nucleation and crystal growth [23,24]. These limitations frequently compromise the maintenance of supersaturation and result in

inconsistent drug release profiles [25,26].

In response to these limitations, ternary solid dispersions (TSDs) have emerged as a promising strategy in pharmaceutical development, consisting of a poorly water-soluble drug dispersed within a matrix composed of two distinct solid excipients.[27] The addition of a third component, such as a secondary polymer, surfactant, or small-molecule stabilizer, into the BSDs system facilitates additional molecular interactions.[28,29] These interactions can enhance physical stability, improve wettability, prolong supersaturation, and optimize drug release kinetics [30,31].

Despite the increasing importance of TSDs in current pharmaceutical development, comprehensive reviews specifically addressing their role in enhancing drug dissolution remain limited. Therefore, this review aims to address that gap by providing a current and focused overview of TSD-based strategies, emphasizing their application in improving the dissolution of poorly water-soluble drugs. Recent studies are systematically summarized and critically analyzed to highlight formulation trends, excipient selection, and mechanistic insights that contribute to the improved dissolution performance through TSD systems.

2. Methodology

This review was based on literature sourced from Scopus, Google Scholar, and PubMed databases using specific keywords: “ternary solid dispersion” and “dissolution.” The inclusion criteria were limited to peer-reviewed original research articles written in English and published between 2020 and 2025. Figure 1 represents a flow chart of methodology.

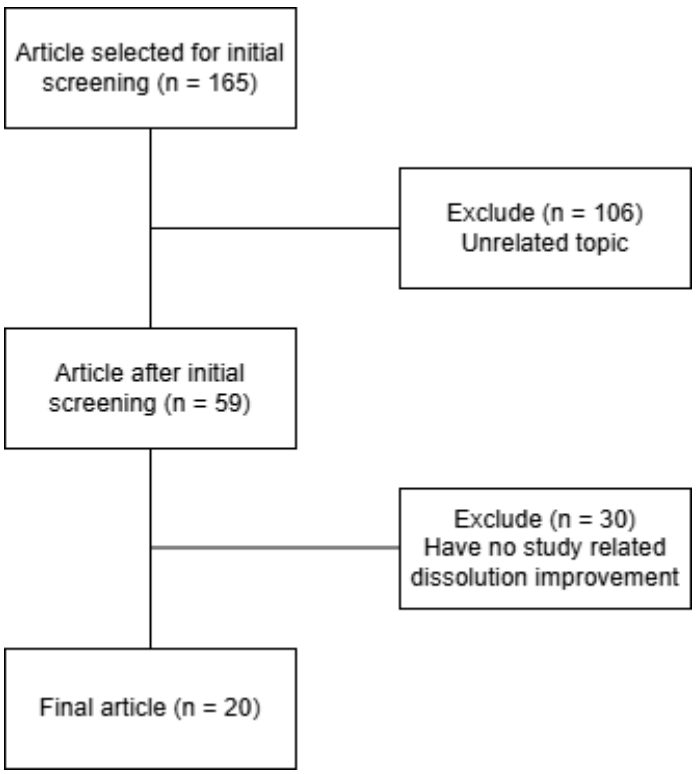

Figure 1. Flow chart of the methodology

3. Dissolution Challenges in Poorly Soluble Drugs

Drugs with low water solubility, particularly those categorized as Class II and IV under the BCS, encounter considerable challenges in oral drug administration. Their poor water solubility limits dissolution in the gastrointestinal (GI) tract, thereby impairing absorption into systemic circulation. For BCS Class IV compounds, this problem is further compounded by low permeability, rendering the development of effective oral formulations especially difficult. In contrast, BCS Class II drugs, although poorly soluble, demonstrate favorable permeability and can achieve sufficient absorption if their dissolution rate is adequately enhanced [32]. Failure to address solubility and dissolution limitations often leads to reduced bioavailability, fluctuating pharmacokinetics, and, in some cases, therapeutic failure or the necessity for elevated dosages that increase the risk of GI adverse effects [33].

Pharmacopeia classifications, such as those outlined in the United States Pharmacopeia, categorize solubility from "very soluble" to "practically insoluble". Compounds with solubility below 1 mg/mL are generally classified as poorly soluble [34,35]. For optimal oral absorption, the drug must meet the "sink condition," indicating the highest dose should dissolve completely in 250 mL of GI fluids [36]. Nonetheless, the majority of poorly soluble drugs fail to achieve this requirement with conventional formulations, highlighting the need for advanced drug delivery strategies to enhance dissolution and bioavailability.

Various formulation strategies have been explored to improve the solubility and dissolution of poorly water-soluble drugs, including chemical modification, particle size reduction, crystal engineering, amorphization, and the use of nanotechnology or liquisolid systems [15,37–39]. Among these, amorphous systems hold particular potential due to their higher Gibbs free energy and lack of long-range molecular order, which collectively contribute to increased solubility and accelerated dissolution compared to their crystalline forms [15]. Nonetheless, amorphous drugs without the presence of stabilizing excipients are extremely susceptible to recrystallization during dispersion and storage, which can compromise their drug performance [18].

In addition to enhancing solubility and initial dissolution rates, maintaining drug supersaturation throughout the dissolution process is essential to ensure sustained absorption. A study by Elkahbaz et al [40] investigated binary solid dispersion (BSD) systems of atazanavir prepared using polyvinylpyrrolidone vinyl acetate (PVPA) under non-sink conditions in biorelevant media, including fasted and fed state simulated intestinal fluids. The formulation achieved complete (100%) drug release, maintained supersaturation for up to 3 hours, and reached a steady-state flux of 6.0 ± 0.5 $\mu g \cdot min^{-1} \cdot cm^{-2}$, which was significantly higher than the amorphous form (1.1 ± 0.1 $\mu g \cdot min^{-1} \cdot cm^{-2}$) and the crystalline form (0.1 ± 0.03 $\mu g \cdot min^{-1} \cdot cm^{-2}$). This underscores the significance of both initial dissolving enhancement and supersaturation maintenance in the formulation of effective oral therapies for poorly soluble drugs.

Although BSD systems offer significant advantages, several formulations have demonstrated limited dissolution performance due to formulation-related challenges. In

particular, inadequate enhancement of wettability can lead to drug agglomeration during dispersion, reducing the effective surface area and hindering uniform drug release [41].

Poor dispersion frequently results in suboptimal dissolution rates and insufficient supersaturation maintenance, ultimately compromising bioavailability [42]. Budiman et al. reported that although the BSD of alpha mangostin (AM) with polyvinylpyrrolidone (PVP) exhibited high amorphous solubility (~14.3 µg/mL), it failed to achieve effective dissolution due to poor wettability, leading to particle agglomeration and inadequate dispersion in the dissolution medium. As a result, AM concentrations remained undetectable even after 150 minutes [43]. To overcome such limitations, TSD systems have been introduced. By adding a third component, TSDs aim to improve wettability, reduce agglomeration, and stabilize the amorphous form, thereby enhancing dissolution kinetics and sustaining supersaturation [29,44].

Fundamentals of Ternary Solid Dispersions

The primary distinction between binary solid dispersions (BSDs) and ternary solid dispersions (TSDs) is based on the quantity of components in the formulation. BSDs consist of only two primary components are used: the active pharmaceutical ingredients (API) and the polymer carrier [45]. BSD formulations emphasize the interaction between the API and polymer to enhance the solubility and stability of the drug [46,47].

TSDs are advanced pharmaceutical formulations comprising three main components: an API, a primary polymer, and a third component, which may include an additional polymer, surfactant, coformer, or other functional excipient [9,29,48–52]. The addition of this third component enhances the system's ability to improve the solubility, dissolution rate, and physical stability of poorly water-soluble drugs by facilitating more effective molecular interactions and reducing the tendency of recrystallization [53,54]. Classification of TSDs has been described through various approaches in the literature, commonly based on the type and function of the third component or the preparation method employed, such as spray drying, solvent mixing, or wet milling [27,29,31,52,55]. TSD formulations have evolved more rapidly than BSDs in response to increasing concerns regarding the solubilization of insoluble drugs [56–59]. However, the rational design of the TSD systems and the elucidation of their dissolution mechanism remain under active investigation [60]. Therefore, understanding the factors that influence the dissolution behavior of TSDs is crucial for optimizing their formulation and maximizing therapeutic efficacy.

Factors Affecting Dissolution

Multiple factors affect the dissolving rate and overall efficacy of TSD. These parameters are crucial in evaluating the efficacy of the drug's release from the dispersion and its subsequent entry into systemic circulation.

Effects of Physicochemical Profile of Drug

The intrinsic solubility of the drug significantly influences its dissolving rate. TSD systems for poorly soluble drugs aim to enhance solubility of poorly water-soluble drugs not only by converting them into an amorphous state, but also through the addition of a third

component [61]. While amorphization increases apparent solubility by disrupting crystal lattice energy, the third component plays an additional functional role by reducing interfacial tension, improving wettability, and preventing drug aggregation [62].

In a study by Gao et al [63] the TSD comprising curcumin, PVP, and poloxamer 188 exhibited markedly enhanced dissolution relative to its BSDs, leading to less agglomeration and increased homogenous dispersion. The TSD formulation achieved a cumulative dissolution over 80% within 60 minutes, compared to less than 40% in the BSD system. The synergistic effects not only accelerate dissolving kinetics but also increase the drug's physicochemical properties, namely regarding wettability, dispersion behavior, and physical stability.

Effect of Polymer Properties

The selection of polymer substantially influences the dissolution rate of the drug. The solubility and molecular weight of the polymer influence the drug release rate [64,65]. Hydrophilic polymers improve dissolution by promoting the wetting and dispersion of the drug in aqueous environments [66].

To enhance the dissolution profile, hydrophilic polymers such as polyvinylpyrrolidone, polyethylene glycol, hydroxypropyl methylcellulose, and poloxamer were employed to molecularly disperse the poorly water-soluble drugs in TSDs. The selection of an optimal polymer was crucial for the creation of effective TSDs, aimed at preventing the recrystallization of amorphous drugs under supersaturated conditions [67]. Additionally, Zoeller et al. documented the dissolution profile of glyburide in BSDs and TSDs. The BSDs of glyburide exhibited fast release, with approximately 55% of the dosage dissolving within 30 minutes. The TSD systems enhanced the dissolving efficacy of glyburide relative to the binary system. The drug release rate was approximately 80%, and the addition of polymer enhanced the formulation's wettability due to its hygroscopic properties, resulting in expedited or immediate drug release [68].

Effect of Co-formers

Co-formers can improve the dissolving rate by diminishing crystallinity or increasing the solubility of the drug in the dispersion. Riekes et al. conducted a study comparing ezetimibe-lovastatin-Soluplus® (EZE-TSD) versus ezetimibe-lovastatin (EZE-BSD). The intrinsic dissolution rates of ezetimibe and lovastatin increase by 18-fold and 6-fold, respectively, in EZE-TSD. The creation of intermolecular hydrogen bonds between Soluplus® and both drugs resulted in a reduction of recrystallization in EZE-BSD and enhanced physical stability [69]. A distinct ternary formulation including ibrutinib (IBR), oxalic acid (OXA), and microcrystalline cellulose (MCC) exhibited enhanced dissolving characteristics relative to crystalline IBR. Ternary IBR-OXA-MCC formulations exhibited cumulative releases of 97.38% after 4 hours, which is 5.33 and 1.65 times greater than those of crystalline and amorphous IBRs, respectively. The acid functions to decrease the pH of the diffusion layer surrounding dissolving particles, thereby enhancing the dissolution rate of IBR [51].

Effect of Surfactants

Surfactants can reduce the surface tension and enhance the wetting of the

drug, resulting in accelerated dissolution [70]. Surfactants change drug precipitation rates, improve membrane permeability, and influence membrane integrity, consequently affecting the dissolution and disintegration of solid dosage forms. They encapsulate hydrophobic drugs by micelle production, enhancing solubility. TSDs improve miscibility, prevent crystallization, and facilitate uniform dispersions. Anionic surfactants, such as sodium dodecyl sulfate (SDS), demonstrated enhanced solubilizing capacity relative to non-ionic surfactants like polysorbate [71]. Gamal et al. demonstrated that Pluronic F68 enhanced the solubility of itraconazole in amorphous solid dispersion systems. While HPMC-based ASD demonstrated 72% dissolving after 2 hours, the TSD had markedly superior dissolution attributed to the surfactant's solubilizing impact [72].

Effect of Manufacturing Process

The technique employed to formulate the TSD, including spray drying, solvent evaporation, melt extrusion, co-milling, or co-precipitation, significantly influences the physical condition of the drug (amorphous or crystalline), the homogeneity of the dispersion, and the performance of the final product [71]. The selection of manufacturing process profoundly affects the physicochemical properties of the TSD, encompassing amorphization, enthalpy relaxation, and potential recrystallization. These factors subsequently influence the stability and the dissolution rate of the drug [73].

Halder et al [74] compared solvent evaporation and freeze-drying methods in the preparation of carvedilol-TSD with poloxamer 188 and Eudragit RSPO. The freeze-dried system demonstrated superior performance, achieving higher dissolution efficiency under both sink (85.3%) and supersaturated (19.2%) conditions, along with greater drug release at 6 hours under supersaturation (23%) compared to solvent evaporation (79.8%, 16.2%, and 19%, respectively) and crystalline carvedilol (51.5%, 6.0%, and 7.5%). Freeze drying produced a more homogeneous amorphous matrix with enhanced dissolution due to rapid solvent removal and improved particle shape. Consequently, selecting a suitable processing technique and formulation strategy is crucial for ensuring the optimal qualities of TSD systems.

Case Studies: Selected Drugs with Ternary Solid Dispersion Systems

Numerous researches have shown enhanced dissolving performance of different drugs through the application of TSD systems, as summarized in Table 1.

Table 1. Selected case studies of ternary solid dispersions (TSDs) to enhance drug dissolution

No.	Active Compound	Main Polymer	Third Component	Method	Dissolution Studies	Ref.
1.	Cefdinir (CEF)	Polyvinylpyrrolidone (PVP) K30	Curcumin	Solvent evaporation	The CEF ternary solid dispersions (CEF-TSD) showed 100% dissolution in 120 minutes, significantly higher than binary CEF-PVP (76.5%) and CEF-curcumin (3.2%).	[75]

2.	Fenofibrate (FEN)	Copovidone	Hydrogenated phospholipids (HPL)	Hot melt extrusion	FEN-copovidone-HPL (FEN-TSD) demonstrated > 80% release in 30 minutes, significantly outperforming nano-milled commercial FEN (Lipidil Supra®), which reached 45% release in 15 minutes. While nano-milled formulations release rapidly at first, the release tends to plateau.	[76]
3.	Curcumin (CUR)	Hydroxypropyl methylcellulose (HPMC) E5	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®)	Solvent evaporation	CUR-HPMC E5-Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (CUR-TSD) significantly enhanced CUR dissolution (91% ± 3.89) compared to pure CUR (10% ± 2.58).	[77]
4.	Furosemide (FUR)	D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS)	PEGylated glycerides/Gelucire® 15/30 (GL)	Freeze-drying	FUR-TPGS-GL (FUR-TSD) showed a markedly improved dissolution profile, achieving a dissolution efficiency (DE) of 84.66%, a dissolution rate constant of 0.1128 min^{-1}, and a T_{50} of just 4 minutes. In contrast, binary systems reached 29.21% efficiency, a 0.0283 min^{-1} rate constant, and T_{50} of 27 minutes, while pure FUR showed only 3.33% efficiency, a 0.0023 min^{-1} rate, and T_{50} beyond 60 minutes.	[78]
5.	Lacidipine (LCDP)	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (S)	PEGylated glycerides 44/14 (GL)	Spray drying	LCDP-S-GL (LCDP-TSD) showed enhanced dissolution (~100%) compared to the binary (~80%) and pure LCDP (~70%), particularly in pH 4.50 acetate buffer and 1% polysorbate 20. While both binary and LCDP-TSD showed similar behavior in phosphate-buffered solution (PBS) buffer.	[79]

6.	Bedaquiline fumarate (BQF)	PVP	TPGS	Solvent evaporation	BQF-PVP-TPGS (BQF-TSD) significantly enhanced dissolution compared to BQF and binary BQF, with 95% release within 15 minutes. Binary solid dispersion of BQF using PVP (BQF-BSD) exhibited a dissolution rate of 98.24 ± 4.27% (DE15 = 64.09) at 15 minutes, which dropped to 62.44 ± 4.93% (DE60 = 79.84) at 60 minutes. In contrast, BQF-TSD showed a dissolution rate of 98.62 ± 2.80% (DE15 = 74.57) and 99.74 ± 1.81% (DE60 = 93.41) at 15 and 60 minutes, respectively.	[80]
7.	Silymarin (SL)	PVP	Poloxamer 188 (PL)	Solvent evaporation, microwave irradiation (MI), and freeze-drying (FD)	Pure SL exhibited a poor release profile with 32.24 ± 3.7% after 120 minutes, while the binary physical mixture showed a higher release (50.12 ± 3.7%). The BSD showed significant improvement, with releases of 90.57 ± 3.6%, respectively. SL-PVP-PL (SL-TSD) further enhanced the release profile, achieving complete drug release (100%) within 60 minutes. SL-TSD achieved maximum release in just 45 minutes, with about 60% released in the first 10 minutes.	[81]
8.	Carbamazepine (CBZ)	PVP	Tryptophan (Try)	Solvent-lyophilization	The dissolution profile of CBZ followed the order CBZ-PVP-Try (CBZ-TSD) > CBZ-PVP > CBZ. Notably, the pure CBZ exhibited a slow release, with less than 50% dissolution within the first 40 minutes. In contrast, CBZ-TSD showed a significantly higher dissolution rate, with a plateau approximately 21% greater than that of CBZ-PVP.	[82]

9.	β-carotene (CAR)	Hypromellose acetate succinate (HPMCAS) HF	Sorbitan monolaurate/Span 20 (SM)	Solvent evaporation	CAR-HPMCAS-SM (CAR-TSD) showed a significant improvement in comparison with the bulk powder especially at pH 6.8 and pH 7.4, with a gradual release over 2 hours reaching equilibrium. However, at pH 1.2, the release was hindered due to solubility limitations.	[83]
10.	Glibenclamide (GLB)	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer	Poloxamer 407 (PL)	Hot melt extrusion (HME)	GLB-TSD exhibited significantly higher drug release (~100% at 90 minutes) than crystalline GLB (~10% at 90 minutes).	[84]
11.	Toltrazuril (TOL)	PEG6000	$Ca(OH)_2$	Solvent-fusion	TOL-TSD exhibited higher dissolution rates compared to binary system of TOL, with TOL-TSD achieving 95.61% drug release over 24 hours, whereas binary system released only 0.12%.	[85]
12.	Docetaxel (DOCE)	β-cyclodextrin (β-CD)	HPMC E5	Freeze-drying	DOCE-TSD exhibited the highest drug release, reaching 45.44% at 48 hours, which is significantly higher than both the binary (40.76%) and pure DOCE (18.32%).	[86]
13.	Glyburide (GLY)	PEG 4000	Sodium lauryl sulfate (SLS)	Solvent evaporation	Only ~27% of GLY dissolved at 60 minutes, while the physical mixture (PM) improved it to 86%. GLY-TSD achieved 100% drug release within 10-20 minutes. After 12 month storages, GLY-TSD showed the highest DE (95.87 ± 9.89%) and the fastest dissolution time (5.00 ± 0.00 min), significantly outperforming pure GLY (DE = 22.88 ± 8.11%; MDT = 50.91 ± 16.82 min) and the PM (DE = 73.13 ± 17.13%; MDT = 29.37 ± 9.25 min).	[87]

14.	Indomethacin (IND)	PEGylated glycerides (GL)	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (S)	Freeze-drying	IND-TSD demonstrated a significantly enhanced dissolution profile, with a DE of 73.34%, a dissolution rate constant of 0.0921 min^{-1}, and a T_{50} of just 6 minutes. In comparison, the binary systems achieved only 36.68% efficiency, a rate constant of 0.0230 min^{-1}, and a T_{50} of 23 minutes. Meanwhile, pure IND exhibited the poorest performance, with a DE of just 3.32%, a rate constant of 0.0051 min^{-1}, and a T_{50} exceeding 60 minutes.	[88]
15.	Irbesartan (IRB)	N-vinylpyrrolidone and vinyl acetate/Kollidon® VA 64 (K)	PVP K30	Solvent evaporation	The IRB-TSD formulation exhibited the highest drug release, reaching 87.31 ± 0.805% in pH 6.8 phosphate buffer and 97.60 ± 0.887% in 0.1 N hydrochloric acid (HCl) after 120 minutes. In contrast, the binary system released 71.21 ± 0.364% in phosphate buffer and 79.75 ± 0.094% in 0.1 HCl within the same period. Meanwhile, the pure IRB demonstrated significantly lower release values, with 46.03 ± 0.141% in 0.1 N HCl and 22.31% ± 0.169% in pH 6.8 phosphate buffer after 2 hours. Notably, within the first 30 minutes, pure IRB released only 36.55 ± 0.915% and 11.00 ± 1.49% in 0.1 HCl and phosphate buffer, respectively.	[89]

16.	Simvastatin (SIM)	Polyoxyl 40 stearate (Myrj 52®)	PEG 12000	Solvent evaporation	More than 90% of the drug was released from the SIM-TSD formulation within the first 20 minutes, showing a significantly enhanced dissolution profile compared to pure SIM (34.67 ± 0.74%) and its physical mixture (42.87 ± 0.52%) ($p < 0.01$). The dissolution efficiency at 30 minutes (DE_{30}) for SIM-TSD reached 82.85 ± 0.08, which is approximately three times higher than that of pure SIM (27.05 ± 0.34) and 2.4 times greater than the PM (33.55 ± 0.50). These outcomes highlight the effectiveness of the TSD system in improving SIM dissolution.	[6]
17.	Rifaximin (RIF)	Magnesium aluminometasilicate (Neusilin® US2	Poloxamer 188	Solvent evaporation	Crystalline RIF exhibited limited dissolution, releasing only about 32% of the drug over 6 hours. In comparison, the binary system achieved approximately 43% release within the same timeframe. Notably, the RIF-TSD significantly enhanced drug dissolution, reaching over 85% in 6 hours.	[90]
18.	MT-102	Poloxamer 407 (P407)	PVP K30	Solvent evaporation	MT-102-TSD demonstrated a marked improvement in indirubin dissolution, achieving over 80% release within the first 30 minutes. In contrast, the pure MT-102 extract released less than 20% of indirubin, and the binary solid dispersion showed approximately 35% release over the same period.	[91]

19.	Quercetin (Que)	HPMCAS	Lysine (Lys)	Solvent evaporation	Que-TSD significantly enhanced dissolution compared to both crystalline Que and binary formulations. Que-TSD exhibited the highest dissolved concentration, reaching 29 µg/mL within 1 hour, indicating the fastest and most efficient release. In contrast, binary systems displayed moderate dissolution (~18-20 µg/mL), whereas crystalline Que reached only about 5 µg/mL.	[92]
20.	Atorvastatin (ATR)	PEG 10000	Poloxamer 188 (P188)	Melting method	ATR-TSD showed the highest drug release, achieving about 85% within 60 minutes. In comparison, the BSD with PEG 10000 showed a 34% increase in DE_{30} compared to pure ATR (20%). Additionally, BSD with P188 resulted in a 40% increase in DE_{30} compared to pure ATR.	[93]

4. Dissolution Profiles of Ternary Solid Dispersion Systems

Dissolution refers to the process wherein a solid drug dissolves in a solvent to form a solution, which is a critical phase in drug absorption and bioavailability [94–96]. Dissolution testing is a critical tool for evaluating the performance of oral drugs, especially those with poor water solubility [97,98]. Ideally, it is conducted under sink conditions, where the dissolution medium can dissolve at least three times the drug dose to maintain a constant concentration gradient [36]. However, this is often unachievable for poorly soluble drugs, leading to limited dissolution and underestimation of bioavailability.

TSDs have emerged as a promising strategy to overcome this limitation by improving solubility and maintaining supersaturation. Non-sink conditions, which better mimic *in vivo* environments by revealing the drug's ability to sustain supersaturation and resist precipitation, commonly evaluate these systems [99]. Compared to crystalline forms and BSDs, TSDs typically exhibit enhanced dissolution due to improved amorphization, wettability, and molecular dispersion within the polymer matrix [100–102]. These theoretical insights are further supported by several case studies highlighting the practical advantages of TSDs in improving the dissolution behavior of poorly water-soluble drugs.

TSD systems consistently demonstrate enhanced dissolution performance compared to crystalline forms and BSDs. Naama et al [75] evaluated the dissolution profiles of cefdinir (CEF) formulated with polyvinylpyrrolidone (PVP) K30 and curcumin (CUR) using solvent evaporation. The resulting CEF-TSDs achieved complete drug release (100%) within 120 minutes, significantly outperforming the binary CEF–PVP system (76.5%) and the binary CEF–CUR dispersion (3.2%), This finding highlights a significant synergistic effect between the polymer and third component in enhancing dissolution. Similarly, Czajkowski et al [76] investigated the TSD system of fenofibrate (FEN) containing copovidone and hydrogenated phospholipids (HPL), prepared via hot melt extrusion. The FEN-TSD exhibited 80% drug release within 30 minutes, notably surpassing the performance of a commercial nano-milled formulation, which reached only 45% release at 15 minutes and plateaued thereafter. These findings underscore the critical role of both component selection and preparation method in optimizing the dissolution behavior of poorly soluble drugs.

Alkathiri et al [81] further evaluated the influence of preparation methods on the dissolution profiles of a TSD system of silymarin (SL) containing PVP and poloxamer 188. The study compared various TSD formulations prepared via solvent evaporation (SE), microwave irradiation (MI), and freeze-drying (FD). The results demonstrated that the method of preparation significantly affected dissolution performance ($p < 0.01$). Among the TSDs, the FD technique showed the fastest and highest release, reaching 100.13 ± 2.2% in just 45 minutes and approximately 60% within the first 10 minutes. In comparison, TSDs prepared via SE and MI achieved 100.84 ± 3.9% and 100.48 ± 4.2% release in 60 minutes, respectively. Moreover, the ternary physical mixture only reached 87.83 ± 3.8% in 120 minutes. These findings underscore the impact of the manufacturing technique on dissolution behavior.

Additional case studies further support these findings. Barghi et al [87] investigated a TSD formulation of glyburide (GLY) using poloxamer 188 and hydroxypropyl methylcellulose (HPMC), which demonstrated a marked enhancement in dissolution performance. While the pure crystalline GLY released only ~27% within 60 minutes, and the physical mixture (PM) improved release to 86%, the TSD achieved complete drug release (100%) within just 10–20 minutes, with a dissolution time of 5.00 ± 0.00 minutes. After 12 months of storage, the GLY-TSD retained its performance, showing the highest dissolution efficiency (95.87 ± 9.89%) and the lowest mean dissolution time (MDT = 5.00 min), significantly outperforming both the pure drug (DE = 22.88 ± 8.11%; MDT = 50.91 ± 16.82 min) and the PM (DE = 73.13 ± 17.13%; MDT = 29.37 ± 9.25 min). These findings underscore the ability of TSD systems to enhance solubility, accelerate dissolution, and stabilize the amorphous form over time, highlighting their promise in improving the bioavailability of poorly water-soluble drugs.

5. Discussion

TSD systems are designed to overcome the dissolution limitations of poorly water-soluble drugs by combining the drug with a hydrophilic polymer and a functional third component, such as an additional polymer, surfactant, co-former, or other excipient. In contrast to BSDs, which offer limited improvement in wettability and dispersion, TSDs enhance physicochemical stability and solubilization through synergistic interactions among their components. This review aims to investigate the dissolution performance of various TSD formulations and elucidate the underlying mechanisms responsible for improved drug release. Across multiple case studies, TSD systems consistently demonstrated superior dissolution profiles compared to both crystalline drugs and their BSD counterparts.

Dissolution testing was employed as a key tool to evaluate the performance of TSD systems. It provides predictive insight into drug release kinetics and potential bioavailability, especially for BCS class II and IV drugs. Many formulations were tested under non-sink conditions to better reflect the *in vivo* environment, particularly the supersaturation dynamics and risk of precipitation commonly associated with poorly soluble drugs. The dissolution behavior of TSDs is influenced by several factors, including the physicochemical properties of the drug, the selection of polymers and third components, and the manufacturing technique used.

The improved dissolution observed in TSD systems can be attributed to a combination of interrelated mechanisms that promote solubility and stabilize the drug, as illustrated in Figure 2. Numerous drugs possess high lattice energy and strong intermolecular interactions, resulting in thermodynamic stability while significantly restricting aqueous solubility and dissolution rates. BSDs attempt to address this by adding hydrophilic polymers that partially disrupt the crystal lattice and convert the drug into a more soluble amorphous form. However, some of BSDs remain a challenge, such as limited wettability, incomplete dispersion, and susceptibility to recrystallization upon exposure to aqueous environments.

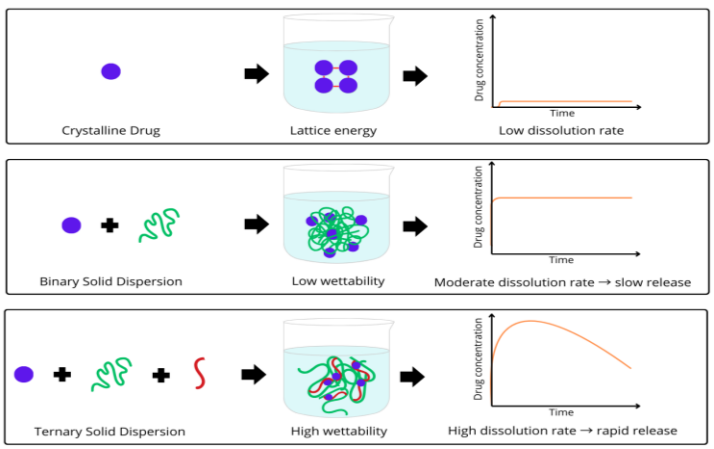

Figure 2. The suggested mechanism for the enhanced dissolution of drugs in ternary solid dispersion systems. The dissolution profile of TSD (bottom)

showed a curved trend, characterized by an initial rapid release followed by a plateau.

TSDs effectively overcome this limitation through the addition of a functional third component, which synergistically interacts with the primary polymer to improve wettability, inhibit nucleation and crystal growth, and stabilize the amorphous form. In addition, molecular-level interactions, particularly hydrogen bonding between the drug and excipients, play a crucial role in preventing phase separation and maintaining the integrity of the amorphous structure. As a result, TSD systems provide enhanced solubility, faster dissolution rates, and improved physical stability compared to both crystalline drugs and BSDs.

The insights presented in this review align with previous studies addressing the dissolution challenges of poorly water-soluble drugs. Elkahbaz et al. [40] demonstrated the critical role of polymer-based amorphous systems in maintaining supersaturation and improving drug dissolution through BSDs. However, despite their advantages, BSDs often exhibit limitations such as insufficient wettability, poor dispersion, and a tendency toward recrystallization, all of which may reduce dissolution efficiency [43]. Building on this foundation, the present review emphasizes that TSD systems, through the strategic addition of a third functional component, achieve superior performance by improving wettability, sustaining supersaturation, and further stabilizing the amorphous form [29,44]. In line with this, the studies reviewed consistently report higher dissolution rates in TSD formulations compared to their BSD counterparts, highlighting the added value and enhanced effectiveness of ternary systems in overcoming solubility and bioavailability barriers.

The method of preparation also plays a critical role in determining the physicochemical characteristics and dissolution behavior of TSD formulations. Techniques such as spray drying, hot melt extrusion, solvent evaporation, freeze-drying, and microwave irradiation affect key factors like the degree of amorphization, particle morphology, porosity, and uniformity of drug distribution. These physical attributes directly impact drug release kinetics. Methods that produce highly porous, fine particles typically improve water penetration and accelerate dissolution, while those yielding dense or aggregated particles may hinder wettability and delay drug release. Furthermore, thermal and mechanical stresses during processing can influence drug–excipient interactions, amorphous stability, and the risk of recrystallization. Therefore, careful selection and optimization of the manufacturing method are essential to fully realize the dissolution-enhancing potential of TSD systems.

This review highlights the importance of rational formulation strategies in the development of effective TSD systems that enhance solubility, dissolution rate, and physical stability by maintaining the drug in an amorphous form. The combination of hydrophilic polymers and functional third components, along with appropriate manufacturing technologies, offers a strong and adaptable platform for delivering poorly water-soluble drugs. Nonetheless, challenges remain, including scalability, long-term physical stability under diverse storage conditions, and the complexity of excipient selection for different drug molecules. Future

research should focus on systematic evaluation of formulation variables, development of predictive models for stability and dissolution behavior, and assessment of in *vivo* performance to ensure clinical translation of *in vitro* outcomes. Addressing these aspects will be crucial for the successful transition of TSD systems from laboratory formulations to commercially viable drug products

6. Author's Perspective

The advancement of TSD technology largely depends on the careful selection of the third component, which not only improves dissolution but also ensures long-term stability and compatibility within formulations. Achieving this requires innovative excipient design grounded in a deep molecular understanding, integrating formulation science with materials chemistry.

Scaling up TSD production from laboratory to industrial levels remains a challenge, necessitating the creation of dependable, scalable manufacturing procedures that continually ensure quality and performance. Beyond enhancing dissolution, TSD systems offer a promising foundation for advanced smart drug delivery systems. Through the integration of controlled release technologies, targeted methods, and combination drugs, TSDs hold enormous promise for advancing personalized drugs and improving therapeutic outcomes.

7. Conclusion

TSD systems enhance the dissolution of poorly water-soluble drugs by inhibiting agglomeration and promoting homogenous dispersion within the dissolution medium. The synergistic interaction between hydrophilic polymers and functional third components improves wettability, stabilizes the amorphous form, and facilitates more efficient drug release. Future research should focus on optimizing the selection of third components, ensuring long-term stability, and enabling scalable production. Furthermore, comprehensive *in vivo* evaluations of TSD formulations are crucial to confirm that improved dissolution translates into enhanced therapeutic efficacy. From a practical perspective, most TSD compositions examined adhere to acceptable unit weight limits, indicating their feasibility for advancement into commercially viable oral dosage forms.

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