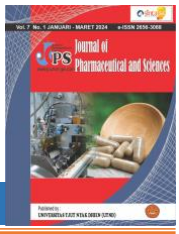
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Solubility Enhancement Strategies for Diflunisal: A Comprehensive Review of Formulation Approaches and Multicomponent Crystals

Strategi Peningkatan Kelarutan Diflunisal: Tinjauan Komprehensif terhadap Pendekatan Formulasi dan Multikomponen Kristal

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Abstract

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) classified as a Biopharmaceutics Classification System (BCS) Class II compound, characterized by high permeability but low aqueous solubility, which limits its dissolution rate and oral bioavailability. Although various strategies have been developed to address this limitation, few reviews have comprehensively compared formulation-based approaches with multicomponent crystal engineering for the same BCS Class II model drug. This narrative review evaluates strategies for improving diflunisal solubility and dissolution based on eleven primary research articles published between 2010 and 2025, supplemented by selected supporting literature. The review focuses on preparation methods, solid-state characterization, and the effects of formulation and crystal modification on physicochemical and biopharmaceutical properties. Formulation approaches, including solid dispersions, particle-size reduction, and Supercritical Antisolvent (SAS) processing, enhanced dissolution through reduced crystallinity and increased surface area. Notably, diflunisal crystallinity was no longer detectable in diflunisal–PVP coprecipitates prepared using SAS. Crystal engineering approaches, including cocrystals, salts, drug–drug crystals, and eutectic systems, modified crystal packing and intermolecular interactions without altering the chemical structure of diflunisal. The diflunisal–nicotinamide (2:1) cocrystal increased intrinsic dissolution rate by approximately 20%, whereas the diflunisal–theophylline cocrystal increased apparent solubility while maintaining an intrinsic dissolution rate comparable to diflunisal. Overall, cocrystallization showed a promising profile, but direct head-to-head comparisons are lacking and most evidence remains in vitro. Further studies should address long-term stability, scale-up, and in vivo performance..

***Keywords:** Diflunisal; Solubility; Crystal Engineering; Cocrystal; Multicomponent crystal.*

Abstrak

Diflunisal merupakan obat antiinflamasi nonsteroid (OAINS) yang termasuk dalam Kelas II berdasarkan Sistem Klasifikasi Biofarmasetika (Biopharmaceutics Classification System, BCS), dengan karakteristik permeabilitas tinggi tetapi kelarutan yang rendah dalam air, sehingga membatasi laju disolusi dan bioavailabilitas oralnya. Meskipun berbagai strategi telah dikembangkan untuk mengatasi keterbatasan tersebut, kajian yang secara komprehensif membandingkan pendekatan berbasis formulasi dengan rekayasa kristal multikomponen pada obat model BCS Kelas II yang sama masih terbatas. Kajian naratif ini bertujuan mengevaluasi berbagai strategi peningkatan kelarutan dan disolusi diflunisal berdasarkan sebelas artikel penelitian primer yang diterbitkan pada periode 2010–2025, dengan didukung oleh sejumlah literatur relevan lainnya. Pembahasan difokuskan pada metode preparasi, karakterisasi keadaan padat, serta pengaruh modifikasi formulasi dan struktur kristal terhadap sifat fisikokimia dan biofarmasetika diflunisal. Pendekatan formulasi, meliputi dispersi padat, pengecilan ukuran partikel, dan metode Supercritical Antisolvent (SAS), terbukti mampu meningkatkan disolusi melalui penurunan derajat kristalinitas dan peningkatan luas permukaan. Secara khusus, kristalinitas diflunisal tidak lagi terdeteksi pada kopresipitat diflunisal–PVP yang dipreparasi menggunakan metode SAS. Sementara itu, pendekatan rekayasa kristal, yang mencakup kokristal, garam, kristal obat–obat, dan sistem eutektik, mampu memodifikasi susunan kristal serta interaksi antarmolekul tanpa mengubah struktur kimia diflunisal. Kokristal diflunisal–nikotinamida (2:1) menunjukkan peningkatan laju disolusi intrinsik sekitar 20%, sedangkan kokristal diflunisal–teofilin mampu meningkatkan kelarutan tampak dengan mempertahankan laju disolusi intrinsik yang sebanding dengan diflunisal murni. Secara keseluruhan, pembentukan kokristal menunjukkan potensi yang menjanjikan sebagai strategi peningkatan sifat biofarmasetika diflunisal. Namun, belum tersedianya penelitian yang membandingkan berbagai pendekatan secara langsung serta masih dominannya bukti yang diperoleh melalui pengujian in vitro menjadi keterbatasan utama. Oleh karena itu, penelitian lebih lanjut diperlukan untuk mengevaluasi stabilitas jangka panjang, kelayakan peningkatan skala produksi, serta kinerja in vivo dari sistem yang dikembangkan.

Kata kunci: Diflunisal; Kelarutan; Rekayasa kristal; Kokristal; Kristal multikomponen.

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Introduction

Poor aqueous solubility remains one of the major challenges in pharmaceutical formulation because it directly affects drug dissolution, oral absorption, and bioavailability [1]. Diflunisal, a salicylic acid derivative widely used as an analgesic and anti-inflammatory agent, is classified as a Biopharmaceutics Classification System (BCS) Class II drug with high permeability but low aqueous solubility, making dissolution the rate-limiting step for its oral absorption [2,3]. Various formulation strategies, including particle size reduction, solid dispersions, lipid-based formulations, nanoparticles, inclusion complexes, salt formation, and cocrystallization, have been developed to improve the solubility and dissolution of diflunisal [3,4]. However, these approaches often face limitations such as physical instability, manufacturing complexity, and storage-related challenges.

Recently, crystal engineering has emerged as a promising alternative for enhancing drug solubility without altering the chemical structure of the active pharmaceutical ingredient. Pharmaceutical multicomponent crystals, including cocrystals, salts, drug–drug crystals, and eutectic mixtures, have demonstrated improvements in solubility, dissolution rate, and solid-state stability through the modification of crystal packing and intermolecular interactions [5,6]. Although several studies have investigated diflunisal multicomponent crystal systems, particularly cocrystals and salts, most reports have focused on individual crystal design strategies rather than providing a comparative evaluation with conventional formulation approaches [7,8,9]. Therefore, this review summarizes and critically evaluates current strategies for improving diflunisal solubility, emphasizing formulation approaches and multicomponent crystal engineering.

Previous reviews have generally discussed pharmaceutical cocrystals from a broad perspective or across multiple drug compounds, focusing on the principles of crystal engineering, preparation methods, and physicochemical properties [22,36]. In contrast, primary studies on diflunisal have mainly investigated individual systems, including cocrystals with nicotinamide, isonicotinamide, theophylline, and pyrazinamide, drug–drug salts, and solid dispersions [10,12,16,17]. Based on the literature search conducted in the databases included in this review, no previous review was identified that specifically compares formulation approaches, including solid dispersions and Supercritical Antisolvent (SAS) technology, with multicomponent crystal engineering approaches, including cocrystals, salts, drug–drug crystals, and eutectic systems, using diflunisal as a common BCS Class II model drug. Such a comparison is important because these approaches improve the biopharmaceutical performance of diflunisal through different mechanisms and may differ in their effects on solubility, dissolution, solid-state stability, scalability, and regulatory considerations. Accordingly, this review extends beyond previous reviews that have primarily focused on pharmaceutical cocrystals. It provides three main contributions: first, a qualitative and quantitative comparison of the available evidence on different strategies for improving the solubility and dissolution performance of diflunisal; second, a mechanistic analysis linking crystal packing, intermolecular synthons, lattice energy, and solubility; and third, a critical evaluation of solid-state stability, manufacturing scalability, and the potential translation of these approaches into pharmaceutical development.

Methods

This study was conducted as a narrative review. This approach was selected because the review aimed to synthesize and critically interpret evidence on various strategies for improving the solubility and dissolution performance of diflunisal. The included studies used heterogeneous designs, formulations, experimental systems, and testing conditions, making a formal quantitative synthesis or meta-analysis

inappropriate [19–21]. Accordingly, this review did not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, did not use a registered review protocol, and did not perform a formal risk-of-bias assessment. A literature search was conducted using Google Scholar, PubMed, and ScienceDirect for publications from 2010 to 2025. The search strategy used the following combination of keywords: "Diflunisal" AND "Solubility" AND "Crystal Engineering." The initial search identified 813 records across the databases. The records were subsequently screened in stages based on title and abstract, followed by full-text assessment, with duplicate records removed during the screening process. Primary evidence was restricted to original research articles published between 2010 and 2025 that focused on diflunisal and addressed solubility enhancement, dissolution performance, or crystal engineering, and for which the full text was available. Review articles, conference proceedings, books, theses, and editorials were excluded from the primary evidence synthesis. Based on these criteria, eleven primary studies were selected as the core evidence for the review (Table 1).

Review articles, regulatory guidelines, and other relevant supporting literature were not considered primary evidence. Instead, these sources were selectively used to provide conceptual, mechanistic, and regulatory context for the interpretation of the primary studies. From the eleven selected primary studies, the following information was extracted: authors, publication year, drug–coformer system or formulation, preparation method, characterization techniques, and principal findings, including quantitative data when reported. The extracted evidence was synthesized using a narrative thematic approach and organized into three main themes: (1) formulation-based approaches, (2) multicomponent crystal engineering approaches, and (3) cross-strategy comparison. Rather than applying a formal risk-of-bias assessment, the strength and interpretability of the available evidence were qualitatively considered based on three aspects: the clarity and adequacy of solid-state characterization, the completeness of the reported solubility or dissolution testing conditions, and the availability of quantitative data. These criteria were used to assess the interpretability and comparability of findings across studies rather than to generate a formal quality score. The limitations associated with this approach are discussed in the Limitations section.

Result and Discussion

Physicochemical Characteristics of Diflunisal as a Poorly Water-Soluble Drug

Diflunisal is a salicylic acid derivative classified as a nonsteroidal anti-inflammatory drug (NSAID). According to the Biopharmaceutics Classification System (BCS), diflunisal belongs to Class II, which is characterized by high membrane permeability but low aqueous solubility. Consequently, its oral absorption is primarily limited by the dissolution process, making the dissolution rate an important determinant of oral bioavailability.

Most of the primary studies included in this review addressed the poor solubility and dissolution rate of diflunisal, which have motivated the development of alternative solid-state forms through both formulation-based and crystal engineering approaches. The objective of improving solubility and oral bioavailability was explicitly reported in studies investigating diflunisal–nicotinamide and diflunisal–isonicotinamide cocrystals [7]. Other studies focused more specifically on improving dissolution performance, either through polymer-based coprecipitation [11] or by evaluating the intrinsic dissolution rate of diflunisal cocrystals [10]. The classification of diflunisal as a BCS Class II drug with low aqueous solubility is supported by primary studies [2,16] as well as broader reviews of BCS Class II drugs [1,3].

In addition to its poor aqueous solubility, diflunisal contains carboxylic acid and phenolic hydroxyl functional groups that can participate in hydrogen bonding as donors and acceptors. These functional groups enable diflunisal to form diverse supramolecular synthons with suitable coformers, providing a structural basis for investigating its solid-state modification through pharmaceutical crystal engineering. Accordingly, several studies have focused on modifying the crystal lattice and intermolecular interactions of diflunisal while preserving the chemical structure of the active pharmaceutical ingredient (API) [7].

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Table 1. Summary of Crystal Engineering and Formulation Strategies for Enhancing the Physicochemical Properties of Diflunisal

No.	Author (Year)	System/Formulation	Preparation Method	Characterization	Key Findings
1	Évora et al. (2011) [13]	Co-crystal Diflunisal–Pyrazinamide (1:1)	Neat grinding, liquid-assisted grinding, thermal activation	DSC, FTIR, PXRD, PLTM	Successfully formed a novel cocrystal through pyridine–carboxylic acid hydrogen bonding, exhibiting physicochemical properties distinct from the parent APIs.
2	Wang et al. (2013) [7]	Co-crystal Diflunisal–Nicotinamide and Diflunisal–Isonicotinamide (2:1)	Solution crystallization	PXRD, DSC, FTIR, LNMR, SSNMR	Enhanced solubility and dissolution rate compared with pure diflunisal, with good thermal stability. Melting points of the DIF–NIC and DIF–ISO cocrystals were 195 and 182 °C, respectively. Kelarutan Meningkat 1,5 dan 3 kali lipat.
3	Évora et al. (2014) [10]	Diflunisal–Nicotinamide (2:1)	Ball milling, solution crystallization	Phase diagram, calorimetry, IDR	Increased intrinsic dissolution rate by approximately 20%; a eutectic composition was also identified in addition to the cocrystal; enthalpic stabilization of the cocrystal was quantified by solution calorimetry, and the ternary phase diagram identified conditions for scale-up.
4	Surov et al. (2014) [15]	Co-crystal Diflunisal–Theophylline	Solution crystallization	SCXRD, DSC, calorimetry, dissolution test	Increased apparent solubility with good stability under different humidity conditions. Intrinsic dissolution rate was comparable to that of pure diflunisal.
5	Bag et al. (2014) [17]	Drug-drug salt Ciprofloxacin–Diflunisal	Liquid-assisted grinding	PXRD, FTIR, DSC, TGA	Successful salt formation according to the ΔpKa rule, resulting in a new crystalline phase.
6	Zahran et al. (2014) [11]	Solid dispersion Diflunisal–PVP	Supercritical Antisolvent (SAS)	SEM, DSC, PXRD, FTIR, dissolution	Reduced crystallinity and particle size, leading to a significant increase in dissolution rate. Diflunisal crystallinity was no longer detected in the coprecipitates, and SAS processing of diflunisal alone yielded a different polymorph.
7	Cuadra et al. (2016) [12]	Co-crystal Diflunisal–Nicotinamide	Supercritical CO_2 Antisolvent	XRD, DSC, FTIR, SEM, dissolution	The SAS process successfully produced cocrystals with faster dissolution than pure diflunisal.
8	Bhattacharya et al. (2018) [16]	Multidrug salt Norfloxacin–Diflunisal	Liquid-assisted grinding	SCXRD, solubility, membrane permeability	Norfloxacin solubility increased at pH 7.4 (except for NOR–MEF), and the NOR–DIF salt showed improved diffusion compared with the parent drugs.
9	Wang et al. (2019) [18]	Co-crystal Diflunisal–Isonicotinamide	Solution crystallization	THz-TDS, Raman, DFT	Confirmed the intermolecular crystal structure and demonstrated the formation of a stable heterosynthon.
10	Wu et al. (2020) [14]	Drug-drug co-crystal Diflunisal–Pyrazinamide	Mechanical grinding	THz-TDS, Raman, DFT	Confirmed the formation of a carboxylic acid–pyridine heterosynthon, supporting structural stability.
11	Rosso et al. (2025) [2]	Supramolecular adduct Diflunisal–Tyramine	Mechanochemistry	SCXRD, SSNMR, PXRD, solubility test	A new polymorph was successfully obtained, showing improved solubility (increased equilibrium solubility determined by solution ^{1}H NMR).

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Conventional Formulation Approaches for Improving Diflunisal Solubilit

Conventional formulation strategies aim to improve the dissolution performance of diflunisal without altering its molecular structure. Among these approaches, solid dispersion using hydrophilic polymers has received considerable attention. Zahran et al. demonstrated that diflunisal–polyvinylpyrrolidone (PVP) systems prepared using the Supercritical Antisolvent (SAS) process produced submicron particles with markedly reduced crystallinity. Diflunisal crystallinity was no longer detectable in the coprecipitates prepared with both PVP K-30 and PVP K-10. The resulting reduction in crystallinity, combined with the increased specific surface area, substantially enhanced the dissolution rate compared with crystalline diflunisal. The SAS process also produced particles with a narrower particle-size distribution than conventional preparation methods. In addition, processing diflunisal without polymer under SAS conditions resulted in a polymorphic form different from that of the starting material [11]. These findings suggest that the improved dissolution performance of the diflunisal–PVP systems may result from the combined effects of reduced crystallinity, particle-size reduction, and molecular dispersion of diflunisal within the hydrophilic polymer matrix. These mechanisms are consistent with the general principles of solid dispersion, in which improved wettability, increased surface area, and the higher free energy of the amorphous state can contribute to enhanced dissolution. However, the physical stability of amorphous or partially amorphous systems remains an important consideration because the drug may undergo molecular rearrangement or recrystallization during storage. The extent of this instability depends on factors such as drug–polymer miscibility, molecular mobility, and storage conditions, particularly temperature and humidity [28,29].

Pharmaceutical Cocrystals as a Crystal Engineering Strategy

Among the strategies identified in the reviewed literature, pharmaceutical cocrystallization was the most frequently investigated approach for improving the physicochemical and dissolution properties of diflunisal. Pharmaceutical cocrystals are designed by constructing a new crystal lattice through non covalent interactions between diflunisal and a suitable coformer while maintaining the chemical identity of the active pharmaceutical ingredient (API). Wang et al. successfully prepared diflunisal nicotinamide and diflunisal–isonicotinamide cocrystals at a 2:1 stoichiometric ratio. Both cocrystals showed higher aqueous solubility and faster dissolution than pure diflunisal. FTIR and solid-state NMR analyses indicated that these changes were associated with the formation of heterosynthons involving the carboxylic acid group of diflunisal and the amide or pyridine functionalities of the respective coformers [7]. The diflunisal–nicotinamide and diflunisal–isonicotinamide cocrystals exhibited melting points of 195 °C and 182 °C, respectively, suggesting relatively high thermal stability compared with lower-melting solid forms [7]. Pallipurath et al. subsequently reported eight new diflunisal cocrystals and examined modifications in diflunisal crystal habit. The study showed that the original diflunisal crystals, which tended to form long and thin needle-like crystals, could be modified through cocrystallization. The presence of N-aromatic coformers also favored the formation of carboxylic acid–N-aromatic heterosynthons over the carboxylic acid homodimer motif, highlighting the role of supramolecular synthon selection in determining crystal packing [8]. More recently, a study of diflunisal piperazine cocrystals investigated different stoichiometric forms, with particular attention to reversible solid-state transformations and their dissolution properties [35]. These findings indicate that coformer identity and stoichiometry can substantially influence the resulting crystal structure and pharmaceutical performance.

Cocrystal preparation has also been investigated using alternative manufacturing techniques. Cuadra et al. prepared diflunisal–nicotinamide cocrystals using the Supercritical Antisolvent (SAS) technique and obtained a crystal structure equivalent to that produced by solution crystallization and liquid-assisted grinding [12]. This finding demonstrates that the SAS process can produce the same cocrystal form as established preparation methods, while offering potential advantages for particle engineering and process development. However, further assessment of process yield, solvent recovery, scalability, and regulatory requirements is necessary before its manufacturing advantages can be established. Évora et al. reported that the intrinsic dissolution rate of the diflunisal–nicotinamide cocrystal was approximately 20% higher than that of pure diflunisal [10]. Although this increase was measurable, its magnitude can be considered moderate. Therefore, the potential value of the cocrystal should not be assessed solely from the percentage increase in dissolution rate. The study also demonstrated the thermodynamic stabilization of the cocrystal relative to its individual components using solution calorimetry. In addition, the ternary diflunisal–nicotinamide–ethanol phase diagram identified compositional regions relevant to crystallization and process development, providing information that may be useful for future scale-up studies [10]. The same study identified a eutectic composition, indicating that eutectic formation may represent an additional solid-state strategy for modifying

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the dissolution behavior of diflunisal. Overall, the performance of diflunisal cocrystals depends on coformer identity, stoichiometry, crystal packing, preparation method, and the physicochemical properties of the resulting solid form.

Drug-Drug Cocrystals and Multidrug Crystal Systems

Recent advances in crystal engineering have extended beyond conventional inert coformers to drug–drug cocrystals, in which two pharmacologically active compounds are incorporated into a single crystal lattice. Évora et al. successfully prepared a 1:1 cocrystal of diflunisal and pyrazinamide, generating a new crystalline phase that combines two pharmacologically active compounds within the same solid form [13]. Beyond its potential implications for solid-state modification, this approach may offer practical advantages for combination therapy by incorporating two active pharmaceutical ingredients into a single crystalline system, although its potential effect on pill burden requires evaluation in the context of the final dosage form and clinical dosing regimen. Wu et al. subsequently investigated the intermolecular interactions in the diflunisal–pyrazinamide cocrystal using terahertz spectroscopy, Raman spectroscopy, and density functional theory (DFT) calculations. Their computational analysis identified the carboxylic acid–pyridine heterosynthon as the most energetically favorable intermolecular interaction, supporting its role in stabilizing the cocrystal structure [14]. These findings further demonstrate how spectroscopic and computational approaches can complement solid-state characterization by linking specific intermolecular interactions to crystal stability. Another drug-drug cocrystal was reported by Surov et al., who developed a diflunisal theophylline cocrystal with increased apparent solubility and good physical stability under different humidity conditions [15]. The incorporation of theophylline also provides a potential basis for combining two pharmacologically active compounds within a single solid form. However, the improved apparent solubility was not accompanied by a corresponding increase in intrinsic dissolution rate. The intrinsic dissolution rate of the cocrystal was reported to be comparable to that of the individual components, indicating that increased apparent solubility does not necessarily translate into enhanced intrinsic dissolution performance [15]. Surov et al. also reported the enthalpy of cocrystal formation and calculated lattice energy for the diflunisal theophylline system [15].

Salt Formation and Multidrug Salts as Alternative Crystal Modification Strategies

Salt formation represents another crystal-engineering strategy for modifying the solid state and solution behavior of poorly water soluble drugs. Unlike cocrystals, salts involve proton transfer between acidic and basic components, resulting in ionic crystalline materials whose aqueous solubility can be strongly influenced by ionization and pH. Bag et al. successfully synthesized a ciprofloxacin diflunisal salt using liquid-assisted grinding based on the ΔpKa rule [17]. Bhattacharya et al. subsequently reported norfloxacin–diflunisal multidrug salts and found that norfloxacin solubility increased at pH 7.4 for the NOR DIF system, while membrane diffusion was also improved compared with the parent drugs [16]. These findings indicate that multidrug salts can modify solution and membrane-transport properties, although the contribution of the diflunisal component and the translation of these in vitro findings to oral bioavailability require further evaluation [16,17].

Characterization Techniques for Diflunisal Multicomponent Crystals

Comprehensive characterization is essential to confirm the successful formation of new crystalline phases. Powder X-ray diffraction (PXRD) was consistently employed to identify unique diffraction patterns corresponding to newly formed crystal structures. Differential scanning calorimetry (DSC) was used to detect new melting points indicative of phase formation, whereas Fourier-transform infrared (FTIR) and Raman spectroscopy provided evidence of changes in intermolecular hydrogen bonding. Single crystal X-ray diffraction (SCXRD) remains the gold standard for elucidating atomic crystal structures. More recently, advanced analytical techniques including terahertz time-domain spectroscopy (THz-TDS), solid state nuclear magnetic resonance (SSNMR), and density functional theory (DFT) calculations have enabled detailed investigation of supramolecular interactions governing crystal formation [18,14,2].

Analisis Mekanistik Peningkatan Kelarutan dan Laju Disolusi

The solubility of a pharmaceutical cocrystal is governed by the balance between the thermodynamic stability of the cocrystal phase and the interactions of its components with the dissolution medium. Cocrystals containing highly water-soluble coformers, such as nicotinamide, may exhibit improved solubility relative to

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the parent drug. However, during dissolution, such cocrystals may undergo conversion to a more thermodynamically stable drug phase. Consequently, the apparent solubility advantage may be transient or kinetically controlled, consistent with the so-called spring and parachute effect, and should therefore be evaluated together with the solid-phase transformation profile [23,25,37]. Similarly, lower lattice energy does not necessarily result in higher solubility because solubility reflects the balance between the energetic cost of disrupting the crystal lattice and the energetic gain associated with solvation in the dissolution medium [23].

This relationship is evident in the diflunisal systems reviewed. Although the diflunisal–nicotinamide (2:1) cocrystal exhibited enthalpic stabilization, its intrinsic dissolution rate increased by only approximately 20% compared with pure diflunisal [10]. Likewise, the diflunisal–theophylline cocrystal increased apparent solubility without producing a substantial change in intrinsic dissolution rate [15]. These findings demonstrate that solubility and intrinsic dissolution rate represent related but distinct properties and do not necessarily change in parallel. They also indicate that a thermodynamically stable cocrystal does not automatically produce a large increase in solubility or dissolution performance. The reported melting points of the diflunisal–nicotinamide and diflunisal–isonicotinamide cocrystals were 195 °C and 182 °C, respectively [7]. However, enthalpy of fusion and lattice energy were not consistently reported across the studies reviewed, limiting direct thermodynamic comparison among the different diflunisal solid forms.

At the molecular level, the carboxylic acid and phenolic hydroxyl groups of diflunisal can participate in hydrogen-bonding interactions with suitable coformers. FTIR and solid-state NMR (SSNMR) analyses indicated the formation of carboxylic acid–pyridine and carboxylic acid–amide heterosynthons in the diflunisal–nicotinamide and diflunisal–isonicotinamide cocrystals [7]. Similarly, DFT calculations for the diflunisal–pyrazinamide cocrystal identified the carboxylic acid–pyridine heterosynthon as the most energetically favorable intermolecular interaction [14]. Crystal structure database analysis further indicated a preference for carboxylic acid–N-aromatic heterosynthons over carboxylic acid homodimers in the presence of suitable N-aromatic coformers [8]. These observations demonstrate that coformer selection can alter the intermolecular interaction network and crystal packing of diflunisal, thereby modifying the energetic and structural characteristics of the resulting solid form. The different formulation and crystal engineering strategies reviewed operate through distinct mechanisms. Solid dispersions can enhance dissolution through reduced crystallinity, including conversion toward an amorphous state, molecular dispersion within a hydrophilic polymer matrix, and particle-size reduction [11,28]. Salt formation can generate an ionized solid form that may interact more favorably with the aqueous medium, although its solubility can be strongly influenced by pH, ionization equilibria, and common-ion effects [16,17,26].

Eutectic systems, in contrast, can reduce the melting point of the system and potentially facilitate dissolution. In the diflunisal–nicotinamide system, the reported phase diagram identified two eutectic compositions in addition to the cocrystal composition [10,27]. The formation of channels or voids within a crystal lattice has also been proposed as a possible mechanism by which water penetration could be facilitated in certain multicomponent crystals. However, the diflunisal studies reviewed did not provide sufficient structural or experimental evidence to support this mechanism. Therefore, such an explanation should be regarded as a hypothesis requiring further investigation rather than as an established mechanism for diflunisal cocrystals

Comparative Evaluation of Solubility Enhancement Strategies for Diflunisal

The literature reviewed indicates that formulation-based approaches and crystal engineering improve the solubility or dissolution performance of diflunisal through fundamentally different mechanisms (Table 2). Formulation techniques, such as solid dispersion and particle-size reduction, primarily enhance dissolution by increasing surface area, improving wettability, and reducing crystallinity, including conversion toward an amorphous state [11,28,29]. In contrast, crystal engineering modifies the solid-state form itself through the formation of cocrystals, salts, drug–drug crystals, or eutectic systems, thereby altering the thermodynamic stability of the crystal lattice and its interactions with the dissolution medium [7,10,15,17,27]. Importantly, none of the eleven studies reviewed directly compared these two strategy groups in a head-to-head study using the same diflunisal formulation, dissolution medium, pH, and experimental method. Therefore, the comparison presented in Table 2 is cross-study and should be interpreted as indicative rather than as a direct assessment of relative efficacy.

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Table 2. Comparative Overview of Strategies for Improving the Solubility and Dissolution Performance of Diflunisal

Strategy	Diflunisal system/model	Preparation method	Main mechanism	Solubility improvement	Dissolution improvement (IDR)	Physical stability	Advantages and limitations	Diflunisal studies
Polymeric solid dispersion (SAS, PVP)	DIF–PVP K-30/K-10 coprecipitates [11]	Supercritical Antisolvent (SAS) using supercritical CO_2 [11]	Reduced crystallinity/amorphization, molecular dispersion in a hydrophilic polymer matrix, particle-size reduction, and improved wettability [11,28]	Not reported as a single fold-increase value	Significantly higher than crystalline diflunisal; diflunisal crystallinity was no longer detectable [11]	Amorphous systems may be susceptible to recrystallization during storage [28,29]	Advantages: substantial dissolution enhancement; relatively mild processing temperature; production of submicron particles with a relatively narrow size distribution. Limitations: potential recrystallization during storage [28,29]; scale-up challenges for SAS processing [33]; residual solvent considerations.	Zahran et al. (2014) [11]
Particle engineering (SAS without polymer)	Pure diflunisal processed without polymer [11]	Supercritical Antisolvent (SAS) using supercritical CO_2 [11]	Particle-size reduction and increased specific surface area; formation of a different polymorphic form [11]	Not reported	Higher than the untreated starting material [11]	A polymorphic form different from the starting material was obtained [11]	Advantages: no chemical modification and no polymeric excipient required. Limitations: polymorphic transformation requires control; scale-up challenges may remain [33].	Zahran et al. (2014) [11]
Cocrystal with non-active coformer	DIF–NIC (2:1) [7,10]	Ball milling; solution crystallization; SAS [10,12]	Formation of the same cocrystal structure obtained by other preparation methods [12]	Approximately 1.5-fold higher than pure diflunisal [7]	Approximately 20% higher than pure diflunisal [10]	Melting point of 195 °C [7]; enthalpic stabilization reported [10]	Advantages: demonstrates the applicability of SAS to cocrystal production and particle engineering. Limitations: quantitative comparison with other preparation methods remains limited.	Wang et al. (2013) [7]; Évora et al. (2014) [10]; Cuadra et al. (2016) [12]
	DIF–INA (2:1) [7,18]	Solution crystallization [7]		Approximately 3-fold higher than pure diflunisal [7]	Not reported	Melting point of 182 °C [7]		Wang et al. (2013) [7]; Wang et al. (2019) [18]

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	DIF–NIC [12]	Supercritical Antisolvent (SAS) using supercritical CO_2 [12]		Not reported	Faster dissolution than pure diflunisal [12]	Equivalent crystal structure to that obtained by solution crystallization and liquid-assisted grinding [12]		Cuadra et al. (2016) [12]
Drug–drug cocrystal	DIF–THP (1:1) [15]	Solution crystallization [15]	Formation of a new crystalline phase; carboxylic acid–pyridine heterosynthon identified as energetically favorable [14]	Apparent solubility increased [15]	Comparable to pure diflunisal [15]	Good physical stability under different relative humidity conditions [15]	Advantages: combines two pharmacologically active compounds in a single crystal. Limitations: solubility and dissolution performance were not quantitatively reported; further pharmaceutical and pharmacokinetic evaluation is required.	Surov et al. (2014) [15]
	DIF–PZA (1:1) [13,14]	Neat grinding/liquid-assisted grinding and thermal activation [13,14]		Not reported	Not reported	New crystalline structure confirmed by terahertz spectroscopy, Raman spectroscopy, and DFT analysis [14]		Évora et al. (2011) [13]; Wu et al. (2020) [14]
Drug–drug salt	CIP–DIF [17]	Liquid-assisted grinding [17]	Formation of a drug–drug solid form with ionic interactions [16]	Not reported	Not reported	New crystalline phase consistent with the ΔpKa-based salt formation approach [17]	Advantages: potential improvement in diffusion and combination of two active compounds. Limitations: the contribution of the diflunisal component to the observed solubility effect could not be determined separately.	Bag et al. (2014) [17]
	NOR–DIF [16]	Liquid-assisted grinding [16]		Norfloxacin solubility increased at pH 7.4;	Not determined; increased diffusion was reported [16]	Not reported		Bhattacharya et al. (2018) [16]

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				diflunisal solubility was not reported separately [16]				
Eutectic system	DIF–NIC; two eutectic compositions identified in addition to the cocrystal [10,27]	Phase-diagram construction using the ternary DIF NIC ethanol system [10]	Melting-point depression without formation of a single new crystal lattice; weaker intermolecular interactions between components [27]	Not reported	Not quantified separately; eutectic compositions were identified [10]	Not reported	Advantages: potentially simple preparation; does not require formation of a new stoichiometric crystal phase. Limitations: solid-state structure is less defined than that of a cocrystal; evidence for diflunisal remains limited.	Evora et al. (2014) [10]
Supramolecular adduct/new polymorphic form	DIF–tyramine [2]	Mechanochemical processing [2]	Formation of a diflunisal–tyramine supramolecular adduct and a new polymorphic form [2]	Equilibrium solubility increased, as determined by solution ^{1}H NMR [2]	Not reported	New polymorphic form obtained [2]	Advantages: mechanochemical preparation with limited solvent use. Limitations: limited pharmaceutical performance data; safety and suitability of the coformer require further evaluation.	Rosso et al. (2025) [2]

Note: DIF = diflunisal; NIC = nicotinamide; INA = isonicotinamide; THP = theophylline; PZA = pyrazinamide; CIP = ciprofloxacin; NOR = norfloxacin; IDR = intrinsic dissolution rate. The reported data were obtained under different dissolution media, pH conditions, and experimental methods.

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Quantitative evidence on the magnitude of improvement remains limited and heterogeneous. The diflunisal–nicotinamide (2:1) cocrystal increased the intrinsic dissolution rate by approximately 20% compared with pure diflunisal [10]. The diflunisal–theophylline cocrystal increased apparent solubility, whereas its intrinsic dissolution rate remained comparable to that of diflunisal [15]. In the diflunisal–PVP solid dispersion prepared using the SAS process, diflunisal crystallinity was no longer detectable and a significant improvement in dissolution performance was reported [11]. However, the magnitude of improvement observed with solid dispersions and cocrystals cannot be compared directly because the studies used different formulations, dissolution media, experimental conditions, and analytical approaches. The two strategy groups also differ in their solid-state stability and process considerations. Amorphous solid dispersions may provide substantial dissolution enhancement but remain susceptible to molecular relaxation and recrystallization during storage, depending on drug–polymer miscibility and environmental conditions [28,29]. Cocrystals, in contrast, possess a defined crystalline structure and may exhibit good physical stability under controlled humidity conditions, as demonstrated for the diflunisal–theophylline system [15]. Diflunisal cocrystals have also been prepared using several techniques, including liquid-assisted grinding, solution crystallization, and SAS processing [7,10,12]. These findings indicate that cocrystallization can offer a combination of dissolution modification, defined solid-state structure, and compatibility with multiple preparation approaches. However, the extent of these advantages remains dependent on the specific coformer, stoichiometry, crystal structure, and processing conditions. Drug–drug crystal systems may provide additional pharmaceutical value by combining two active compounds within a single solid form and, in some cases, modifying physicochemical properties relevant to diffusion or permeation [16,17]. Meanwhile, SAS should be considered not only as a formulation technique for producing solid dispersions but also as a particle and crystal engineering platform that has been applied to both diflunisal–PVP systems and diflunisal cocrystals [11,12]. Its potential advantages in particle-size control and process conditions therefore extend beyond a single formulation strategy. Overall, the available evidence suggests that rational crystal engineering combined with particle engineering may provide a complementary approach to improving the biopharmaceutical performance of diflunisal. However, the current evidence does not support a definitive ranking of the strategies because direct comparative studies are lacking and the reported experimental conditions are heterogeneous. Future studies should therefore evaluate selected formulation and crystal-engineering approaches under standardized dissolution conditions and assess their physical stability, scalability, and in vivo performance before their relative pharmaceutical advantages can be established.

Conclusions

Low aqueous solubility remains a major limitation to the biopharmaceutical performance of diflunisal. Based on the eleven primary studies narratively reviewed, formulation-based approaches, including solid dispersion and particle engineering using the Supercritical Antisolvent (SAS) process, can enhance dissolution by reducing crystallinity and particle size. In contrast, crystal engineering approaches, including cocrystals, salts, drug–drug crystals, and eutectic systems, modify the solid-state structure and intermolecular interactions of diflunisal, thereby altering its solubility and dissolution behavior. Among the approaches reviewed, pharmaceutical cocrystallization showed a promising overall profile in terms of modifying solubility or dissolution, maintaining a defined crystalline solid state, and offering multiple preparation options. This was particularly demonstrated by the diflunisal–nicotinamide cocrystal, which exhibited an approximately 20% increase in intrinsic dissolution rate and good thermal stability and could be prepared using liquid-assisted grinding, solution crystallization, and SAS [7,10,12]. However, this interpretation remains qualitative because no study directly compared the reviewed strategies under standardized experimental conditions. The magnitude of improvement also varied according to the coformer, solid-state form, preparation method, and dissolution conditions, while most available evidence was generated from in vitro studies.

Future research should focus on four main areas: (i) in vivo pharmacokinetic and bioavailability studies of diflunisal cocrystals to determine whether improvements in dissolution and solubility translate into enhanced systemic exposure; (ii) long-term and accelerated stability studies to characterize the risk of phase transformation, recrystallization, or other solid-state changes under relevant storage conditions; (iii) process development and scale-up studies to evaluate the reproducibility, yield, manufacturability, and process

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robustness of promising crystal-engineering and particle-engineering approaches; and (iv) standardized head-to-head comparisons of formulation and crystal-engineering strategies using the same diflunisal material, dissolution medium, pH, temperature, and analytical methodology. This review has several limitations. First, it employed a narrative rather than systematic review methodology and therefore did not include a formal risk-of-bias assessment. Second, the number of primary studies that met the predefined criteria was limited to eleven. Third, substantial heterogeneity existed among the studies in terms of formulation or crystal system, preparation method, characterization techniques, dissolution or solubility testing conditions, and reported outcome measures. These differences limited direct quantitative comparison across strategies. In addition, most available evidence was derived from in vitro experiments, with limited information on long-term stability, scale-up, and in vivo performance. Therefore, the conclusions should be interpreted as an evidence-based qualitative synthesis rather than as a definitive determination of the relative superiority of any single strategy.

Conflict of Interest

The author declares that there are no conflicts of interest regarding the design, implementation, analysis, or reporting of this study. All research processes were conducted objectively and independently, without any external interference.

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