International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 6s,2025
https://www.theaspd.com/ijes.php

Cutting-Edge Strategies To Enhance The Bioavailability Of Naringenin

Koteswararao Balaga
(ORCID ID: 0009-0006-4430-4913)
PhD student
Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam – 603103, Tamil Nadu, India
Email: koteswararaobalaga@gmail.com

Dr. Priyanka Sinha
(ORCID ID: 0000-0003-2511-0962)
Professor, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education,
Kelambakkam – 603103, Tamil Nadu, India

Dr. Lakshmi K
(ORCID ID: 0000-0002-2460-0073)
Professor and Dean, Chettinad School of Pharmaceutical Sciences,
Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education,
Kelambakkam – 603103,Tamil Nadu, India

ABSTRACT
One of the significant concerns in drug development is the low water solubility of many drugs or active pharmaceutical ingredients (APIs), which hinders their absorption and bioavailability. Co-crystallization and nanotechnology have emerged as a promising strategy to resolve these issues by modifying the physicochemical properties of APIs without altering their pharmacological action. Pharmaceutical co-crystals are formed of an API and one or more co-formers, bind together by non-covalent interactions. This technique can be integrated with another solubility-enhancing strategies called nanotechnology to address the challenges of poor solubility. These techniques can increase solubility, dissolution, stability, and bioavailability, eventually improving drug delivery and efficacy. Various co-crystal formation methods and co-formers, including nicotinamide, succinic acid and amino acids, have shown considerable success in enhancing the therapeutic performance of APIs. Naringenin, a naturally occurring flavonoid, exhibits significant biological activities, including antioxidant, anti-cancer and anti-inflammatory effects. However, its therapeutic potential is often limited due to poor aqueous solubility and permeability, resulting in low bioavailability (approximately 15% in humans). Moreover, the integration of co-crystal technology with nanosuspensions can create a synergistic effect, where the enhanced dissolution and stability of co-crystals are further improved by the reduced particle size and increased surface area provided by nanosuspensions. This combined approach has the potential to significantly increase the bioavailability and therapeutic effectiveness of challenging APIs like naringenin. This comprehensive review attempt explores the advantages of co-crystals integrating with nanotechnology in improving the solubility and bioavailability of poorly water-soluble drugs and aim to demonstrate their capability to transform pharmaceutical formulations and optimize drug delivery systems.
KEYWORDS: *Naringenin, Nanosuspensions, Co-crystals, Bioavailability, solubility*

INTRODUCTION

A major challenge in developing new drugs or formulation lies in achieving sufficient aqueous solubility. To maximize bioavailability a drug should be water-soluble and able to navigate the body's natural barriers effectively. Poor physicochemical qualities, including low chemical stability, dissolution, hygroscopicity and solubility can diminish API's pharmacological efficacy [1]. These limitations also

complicate formulation processes and post-formulation events like absorption, distribution, metabolism and excretion, sometimes even leading to undesirable pharmacological effects and toxicity [2].Initially focused on nano-sizing particles to increase surface area and solubility, nanotechnology has since evolved to encompass more sophisticated strategies such as nanosuspensions, lipid-based nanoparticles, co-crystals, polymeric micelles and dendrimers. These advances have created pathways for improving not only solubility but also targeted drug delivery and controlled release [3]. When combined with co-crystal technology, nanotechnology provides an additional layer for enhancing drug efficacy and stability. For example, nano-co-crystals can be engineered to improve solubility and absorption while maintaining the advantages of traditional co-crystals [4].Co-crystals emerged as a promising approach in the 1990s when M.C. Etter highlighted the potential of hydrogen bonds in multi-component crystallization design [5]. As an outcome of the pharmacological benefits that co-crystals show, there has been a growing interest from the pharmaceutical industry [6].Since then, co-crystals have attracted significant attention due to their ability to modify physical and chemical API properties without altering pharmacological activity [7]. Co-crystals are solid crystalline substances made of two or more dissimilar molecules, with at least one being an API and other being an inactive substance called co-former (excipient) or another API [8]. Co-crystals are crystalline materials, meaning they have a well-ordered and repeating arrangement of molecules. The co-formers are pharmacologically inert but enhance the properties of the API. The components of co-crystals are held together in a specific stoichiometric ratio by non-covalent interactions like hydrogen bonding, ionic bonds, van der Waals forces, or π-π stacking [9–11].Unlike salts, which depend on oppositely charged ions (acid and base combinations) to form, co-crystals don't require this type of chemical reaction. This means that drugs that cannot form salts (non-ionizable drugs) can be made into co-crystals [6]. Co-crystals made from APIs have specific shapes and internal arrangements. It's widely known that crystalline APIs have clear external and internal structures. The internal structure shows how molecules are arranged in the crystal lattice and relates to polymorphism [12].By altering the physicochemical characteristics of the API without changing its chemical structure, co-crystals can lead to potential enhancements in drug properties like solubility, stability, dissolution rate and bioavailability of poorly water-soluble APIs [13]. They also improve the stability of photosensitive or hygroscopic APIs. This offers the potential for enhancing drug delivery and efficacy [11].These improvements in drug properties have led to growing interest from the pharmaceutical industry. Co-crystals can improve the physical and chemical stability of APIs, protecting them from degradation due to environmental factors like moisture, light and heat. They can also alter the melting point, hygroscopicity and mechanical properties of the API, making it more suitable for formulation into various dosage forms [14].To date, numerous co-crystal formulation processes have been established, the most widespread and primary approaches includes gradual evaporation at normal temperature, cooling co-crystallization, liquid-assisted grinding and slurry co-crystallization. Newer approaches, includes ultrasound-assisted co-crystallization and vapor catalytic co-crystallization [13].

ADVANTAGES OF CO-CRYSTALS IN PHARMACEUTICALS

Co-crystals in pharmaceuticals offer several advantages, enhancing the properties of APIs and improving drug delivery.

1. Enhanced solubility: By modifying the crystal lattice structure, co-crystals can increase the solubility of poorly water-soluble APIs, which leads to better absorption and effectiveness in treatment [9].

Example: Atorvastatin calcium solubility was increased by co-crystals formulation using citric acid and nicotinamide [1].

Carbamazepine co-crystals with nicotinamide have shown a remarkable increase in solubility compared to pure carbamazepine [15].

Carbamazepine, an anti-epileptic drug with poor water solubility, has shown improved solubility when formed into co-crystals with saccharin [16].

Zoledronic acid an anti-resorptive agent solubility was increased by co-crystals form with DL-tartaric acid and nicotinamide [17].

2. Improved dissolution rate: By forming co-crystals, the dissolution rate of a drug can be enhanced, which is critical for achieving speedy onset of action.

Example: Glipizide co-crystals prepared with benzoic acid, malonic acid, oxalic acid, and stearic acid resulted in increased dissolution [12].

Valsartan co-crystals with succinic acid improved aqueous solubility and dissolution behavior [18].

3. Improved Bioavailability

Enhanced solubility and dissolution rates from co-crystals lead directly to improved bioavailability, ensuring that a higher amount of the drug reaches systemic circulation.

Example: Naringenin co-crystals with nicotinamide demonstrate higher bioavailability compared to the pure form of naringenin.

4. Improved stability: Co-crystals can often exhibit enhanced stability compared to the pure API, protecting the drug from degradation due to factors like humidity, temperature and light [11].

Example: Fluoxetine hydrochloride co-crystallizes with three different coformers: succinic acid fumaric acid, and benzoic acid. Comparing the three, fumaric acid exhibits better stability in humid environments [19].

Theophylline's using a citric acid co-former forms a co-crystallization state which results in increased physical stability, solubility and bioavailability [20].

4. Reduced hygroscopicity: Co-crystals can reduce the hygroscopic nature of some APIs, making them easier to handle and store, preventing the APIs from degradation, caking and poor flowability.

Example: Oxymatrine, which is used to treat Hepatitis B, is co-crystallized with urea, sulfanilamide, theophylline, 2-ketoglutaric acid and 3-hydroxy-2-naphthoic acid, additional hydrogen bonds are formed, which increases Oxymatrine's hydroscopic stability [21].

Ammonium dinitramide co-crystals were formed with seven co-formers could reduce hygroscopicity [22].

Isosorbide is an effective hyperosmotic agent and highly deliquescence. Its deliquescence was reduced with four cocrystals like piperazine, 3,5-dihydroxybenzoic acid, hydrochlorothiazide, and gallic acid [23].

5. Modified physicochemical properties

Co-crystals can modify properties like melting point, hygroscopicity and mechanical behavior, making the API more suitable for various formulation processes.

Example:

Theophylline co-crystals with apigenin and daidzein improves theophylline physicochemical characteristics, dissolving capacity and bioavailability [24].

Example: Paracetamol co-crystals with oxalic acid have a different melting point and better compressibility, aiding in tablet formulation.

6. Enhanced Permeability

Some co-crystals can improve the permeability of APIs across biological membranes. Enhanced permeability ensures that a larger proportion of the drug can be absorbed, leading to increased bioavailability.

Example: Enrofloxacin (antibacterial agent) with p-nitrobenzoic acid in co-crystal form results in improved solubility, hygroscopicity and permeability [25].

7. Tunable Release Profiles

Co-crystals can be designed to modify the release profile of a drug, providing either immediate or sustained release, depending on therapeutic needs.

Example: Numerous types of co-crystals, nano-co-crystals and co-crystal-loaded nanocarriers have shown significant potential in the fight against cancer through enhanced pharmacokinetic capabilities, decreased toxicities and enhanced physicochemical properties. Via improved penetration and retention, these structures additionally show controlled cargo release and passive targeting [26].

8. Enhanced tabletability: Co-crystals often exhibit better compressibility and flowability compared to the pure API, facilitating tablet formation and improving drug product manufacturability.
Example: Paracetamol (antipyretic drug) with trimethyl glycine exhibits improved tabletability [27].
9. Taste Masking: By incorporating taste-masking agents as co-formers, the unpleasant taste of certain drugs can be reduced, enhancing patient compliance.
Example: Propiverine (to treat bladder problems) has a bitter taste. Propiverine crystalline complexes was made with nine new types of complexes among 42 different substances. Propiverine with salicylic acid crystalline complexes, tasted less bitter than the pure Propiverine [28].

Co-former
Co-formers are essential components in the preparation of co-crystals, as they interact with the API to form a stable crystalline structure. The choice of co-former is critical and it is typically based on factors like compatibility with the API, safety and the ability to form strong, non-covalent interactions.

MOST COMMONLY USED CO-FORMERS FOR PREPARING CO-CRYSTALS
Nicotinamide (Vitamin B3)
Nicotinamide, also known as vitamin B3, is a widely used co-former in pharmaceutical co-crystals due to its strong hydrogen bonding capabilities, making it effective in enhancing the solubility, stability and bioavailability of various APIs. Its amide and pyridine functional groups allow it to interact favorably with a range of APIs, leading to improved drug properties, such as the solubility enhancement seen in co-crystals of carbamazepine and naringenin [29]. Nicotinamide is generally recognized as safe (GRAS), which simplifies regulatory approval for formulations containing it [30].Nicotinamide is compatible with a variety of APIs, making it a versatile co-former. It has been successfully used to create co-crystals with APIs across different therapeutic categories [31]. Additionally, nicotinamide co-crystals can control polymorphism and modify crystal habits, contributing to better manufacturability of drugs [32]. However, nicotinamide is safe at standard doses, excessive use could pose risks and it may not be compatible with all APIs, requiring careful selection during formulation development. Overall, nicotinamide's versatility and pharmaceutical benefits make it a valuable co-former in drug development. Nicotinamide-based co-crystals are shown in Table 1.

Table 1 Nicotinamide-based co-crystals

Drug	Co-former	Improved properties	Reference
Carbamazepine	Nicotinamide	To improve solubility and dissolution	33–37
Niclosamide	Nicotinamide	Treating lung cancer	38
Simvastatin	Nicotinamide	Improve simvastatin solubility	39,40
Fenofibrate	Nicotinamide	Improves fenofibrate dissolution rate	41
Efavirenz	Nicotinamide	Antihyperlipidemic activity	42
Ticagrelor	Nicotinamide	Tableting performance	43
Baicalein	Nicotinamide	Improve oral bioavailability	44
Ferulic acid	Nicotinamide	Improve solubility	45
Mefenamic acid	Nicotinamide	Improve solubility and oral bioavailability	45
Theophylline	Nicotinamide	Improve solubility	46
Asenapine maleate	Nicotinamide	Co-crystal formation	47,48
Ibuprofen	Nicotinamide	Co-crystal formation	49
Lenalidomide	Nicotinamide	Improve solubility	50
Indomethacin	Nicotinamide	Improve solubility	51
p-Coumaric acid	Nicotinamide	Improve solubility and stability	52

Flufenamic acid	Nicotinamide	Co-crystal formation	53,54
Acetaminophen	Nicotinamide	Co-crystal formation	55
Aceclofenac	Nicotinamide	Improve compaction performance	56
Azilsartan	Nicotinamide	Co-crystal formation	57
Carbamazepine	Nicotinamide	Co-crystal formation	58
Niclosamide	Nicotinamide	Improve solubility	59

Carboxylic acid
Carboxylic acid-based co-crystals are shown in Table 2.

Table 2 Carboxylic acid-based co-crystals

Co-crystal	Carboxylic acid Used	Reference
Ibrutinib-Carboxylic acid	Aliphatic acids, Hydroxy-2-naphthoic acids, Mono-hydroxybenzoic acids,	13
Sulfamethazine-Carboxylic acid	2,4-Dihydroxybenzoic acid, 4-Hydroxybenzoic acid, 3,4-Dichlorobenzoic acid, Fumaric acid, Sorbic acid, 1-Hydroxy-2-naphthoic acid, 3-Hydroxy-2-naphthoic acid	60
Isoniazid-Carboxylic Acid	Benzoic acid, Sebacic acid, Suberic acid, Cinnamic acid	61
Isoniazid-Aromatic Carboxylic acids	p-Nitrobenzoic acid (PNBA), p-Cyanobenzoic acid (PCNBA), p-Aminobenzoic acid	62
Meloxicam-Carboxylic acid	Glutaric acid, l-Malic acid, Salicylic acid, Fumaric acid, Succinic acid	63
Sulfathiazole-Carboxylic acids	Glutaric acid, Oxalic acid, l-Tartaric acid, dl-Malic acid, Citric acid	64
Sulfathiazole with Carboxylic acid	-	65
Fluconazole-Aromatic Carboxylic acids	Vanillic acid, 4-Hydroxybenzoic acid	66
Piroxicam-Carboxylic acids	-	67
Axitinib-Carboxylic acids	Fumaric acid, Suberic acid, trans-Cinnamic acid	68
Salicylamide and Ethenzamide with Aromatic Carboxylic acids	-	69
Ketoconazole-Dicarboxylic acid	Fumaric acid, Succinic acid	70
Carbamazepine-Malonic Acid	Malonic acid	71
Carbamazepine with aromatic carboxylic acids	2,3-Dihydroxybenzoic acid, 1-Naphthoic acid, Anthracene-9-carboxylic acid	72
Minoxidil-Carboxylic acid	-	73
Emtricitabine with aromatic carboxylic acids	meta-Hydroxybenzoic acid, Vanillic acid, Ferulic acid, para-Methyl benzoic acid, para-Chlorobenzoic acid, para-Nitrobenzoic acid	74
Ethenzamide with Aliphatic Dicarboxylic acids	Glutaric acid, Malonic acid, Maleic acid	75
Ethenzamide with Aromatic and aliphatic carboxylic acids	4-Aminobenzoic acid, Salicylic acid, 2-Chloro-4-nitrobenzoic acid, Vanillic acid, 4-Hydroxybenzoic acid, Fumaric acid	76

Succinic Acid

Succinic acid is a widely utilized co-former in pharmaceutical co-crystallization due to its strong hydrogen bonding capability, facilitated by its two carboxyl groups. This allows succinic acid to interact effectively with a variety of APIs, resulting in the development of stable co-crystals that suggestively enhance the solubility, dissolution rate and overall bioavailability of poorly soluble drugs [77]. Additionally, succinic acid improves the physio-chemical stability of the co-crystals, making the drugs more resistant to environmental factors. Its compatibility with a wide range of APIs and recognized safety profile further establish its importance in drug development, where it is used to create co-crystals with improved therapeutic performance and easier regulatory acceptance [78]. Succinic acid-based co-crystals are shown in Table 3.

Table 3 Succinic acid-based co-crystals

Drug Component	Co-former	Improved Properties	Reference
Carbamazepine	Succinic acid	*In vitro* and *in vivo* performance	14 79
Atorvastatin calcium	Succinic acid	Solubility and dissolution	80
Carbamazepine	Succinic acid		81
Loratadine	Succinic acid	Solubility	82
Imidazopyridazine	Succinic acid		83
4-Aminobenzoic acid	Succinic acid		84
Piperine	Succinic acid		85
Itraconazole	Succinic acid	Solubility	86
Ketoprofen	Succinic acid, Saccharin	Solubility	87
Fluconazole	Succinic acid, Urea		88

Amino acids

Amino acids are increasingly being explored as co-formers in the creation and development of co-crystals. From a structural point, amino acids are attractive co-former because it contains functional groups (amine and carboxylic acid). It can create hydrogen bonding and boost stabilization via zwitterionic molecules, that encourage stronger bonding which makes them excellent candidates for co-former molecules. These functional groups can participate in various non-covalent interactions, resulting in the development of stable co-crystals. Since amino acids are water-soluble and stable, they also support eco-friendly co-crystallization methods [89]. Amino acid-based co-crystals are shown in Table 4.

Table 4 Amino acid-based co-crystals

Drug	Amino Acid(s)	Purpose (reference)	References
Ibuprofen	(glycine, L-alanine and L-proline)	Increase solubility	90
Ebastine	(L-prolin, L-histidin and asparagine)	Increase solubility	91
Telmisartan	(L-Lysine)	Solubility enhancement	92
Lamotrigine	(L-proline)	Improve dissolution rate	93
Sinapic acid	(arginine, histidine, lysine, tryptophan and proline)	Improve solubility	94
Diclofenac	(L-proline)	Improve solubility and stability	95

Hesperidin	(L-arginine, glutathione and glycine)	Improve solubility, antioxidant and anti-inflammatory activities	96
Posaconazole	(l-glutamine)	Improving solubility and oral bioavailability	97
Indomethacin	(lysine and histidine)	Improve solubility	98

COCRYSTAL OF NARINGENIN

Zeng et al. [99] investigated Naringenin-Norfloxacin co-crystal, focusing on its solubility improvement, antibacterial and anticancer actions. The cocrystal were formulated using crystal transformation technique demonstrated improved Norfloxacin antibacterial activity towards a gram-positive bacterium (*S. aureus*), three gram-negative bacteria (*E. coli*, *D. bacillus*, *P. aeruginosa*) and a fungus (*C. albicans*). The cocrystal formation also increased Naringenin solubility, minimized the hygroscopic nature of Norfloxacin and improved Naringenin anticancer effectiveness towards human breast cancer cells (MDA-MB-231).Oliveira et al. [100] developed a Naringenin-Betaine (co-former) cocrystal using the gas antisolvent technique for *in vitro* permeation studies. This cocrystal enhances both the solubility and dissolution rate of Naringenin, potentially increasing its oral bioavailability. Viability studies on IEC-6 cells indicate that frequent administration of low doses of the cocrystal is needed for effective and safe absorption. The study also suggests a synergistic effect between Naringenin and Betaine in the cocrystal and physical mixture, improving Naringenin's permeation through the blood-brain barrier. Their findings emphasize the possibility of the Naringenin-Betaine cocrystal enabling brain-targeted release of Naringenin following oral administration.Xie et al. [8] focused on ensuring the quality of a Naringenin-Carbamazepine drug-drug cocrystal by developing a quantitative analytical method that integrates Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR) and Raman spectroscopy with chemometric techniques. In their research, the structure of Naringenin-Carbamazepine was confirmed and characterized using single crystal X-ray diffraction (SCXRD), Powder X-ray diffraction (PXRD), IR, Raman and differential scanning calorimetry (DSC) techniques. Hirshfeld surface analysis was employed to further investigate the intermolecular interactions within the eutectic between Naringenin and Naringenin-Carbamazepine. To ensure quality control of Naringenin-Naringenin-Carbamazepine, vibrational spectroscopies (ATR-FTIR and Raman) combined with partial least squares and principal component regression were effectively utilized for the simultaneous quantification of Naringenin, Carbamazepine and Naringenin-Carbamazepine in ternary mixtures.Zhang et al [101] developed co-crystals of Naringenin and Isonicotinamide to investigate their impact on the anti-abdominal aortic aneurysm (AAA) efficacy of Naringenin, using an elastase-induced AAA mouse. Their findings showed that the Naringenin-Isonicotinamide formulation significantly improved the dissolution rate of Naringenin, with a 1.97-time rise in $AUC_{(0-\infty)}$ and an 18-time increase in Cmax, compared to the crude drug. Incorporating PVP or HPMC into the Naringenin-Isonicotinamide co-crystal further enhanced the bioavailability of Naringenin. *In vivo* pharmacodynamic studies demonstrated that Naringenin-Isonicotinamide with HPMC notably boosted Naringenin's inhibitory effects against AAA, leading to better absorption and protective effects on the aorta. HPMC's supersaturation-prolonging impact enhanced the absorption and anti-AAA properties of the Naringenin-Isonicotinamide co-crystal.Srinivas et al. [102] successfully developed Azithromycin co-crystals with Nicotinamide and Naringenin as co-formers to enhance the solubility of Azithromycin through co-crystallization techniques. The co-crystals were produced in 3 different proportions (1:1, 1:2 and 2:1) using dry grinding and solvent evaporation methods. The produced co-crystals were verified using FTIR, DSC and PXRD analyses. The Azithromycin-Nicotinamide co-crystal in a 1:1 ratio, formulated by dry grinding technique, demonstrated a 6.85-time increase in solubility compared to the pure Azithromycin. Similarly, the Azithromycin-Naringenin co-crystal in a 1:1 ratio, produced by the solvent evaporation

technique, showed a 3.06-time increase in solubility compared to the pure Azithromycin.Xu and colleagues [103] investigated the pharmacokinetics and bioavailability of the Naringenin-Nicotinamide cocrystal, which has enhanced solubility. They formulated the cocrystal by solvent evaporation method. In their study, rats were given oral doses of Naringenin, physical mixture of Naringenin-Nicotinamide and cocrystals of Naringenin-Nicotinamide. Their findings indicated that the Naringenin-Nicotinamide cocrystal had a 175.09% higher relative bioavailability than Naringenin alone. The maximum concentration (C_{max}) was 8.43 folds greater for Naringenin and 2.06 folds greater for Naringenin-Nicotinamide. The time to reach maximum concentration (T_{max}) was reduced from 29.4 min to 5.4 min, the clearance decreased from 91.1 L/hr/kg to 49.1 L/hr/kg and the half-life ($t_{1/2}$) increased from 5.37 hours to 8.24 hours. These findings indicate that Naringenin-Nicotinamide cocrystal enhances the bioavailability of Naringenin, leading to faster absorption and slower elimination.Jiang and colleagues [104] developed a Naringenin-Isonicotinamide cocrystal to enhance Naringenin's inhibitory effects on nonalcoholic fatty liver disease (NAFLD) in mice. Naringenin cocrystal was synthesized using a solvent volatilization method. When administered at a dose of 50 mg/kg, the Naringenin-Isonicotinamide cocrystal demonstrated a significantly higher in vitro release rate and increased gastrointestinal absorption in vivo compared to the crude Naringenin. This led to a more pronounced reduction in triglyceride accumulation in the mice. Yin et al. [105] explored slow-release API—API cocrystals of the anticancer drug Oxaliplatin using flavonoids (Baicalein and Naringenin) to delay hydrolysis and reduce toxicity. They successfully synthesized two novel cocrystals, Oxaliplatin-Baicalein and Oxaliplatin-Naringenin, using solution crystallization or solvent-involved grinding methods. These cocrystals were thoroughly characterized using techniques such as SCXRD, PXRD, TGA-DSC and FTIR. The dissolution profiles revealed that both Oxaliplatin-Baicalein and Oxaliplatin-Naringenin cocrystals exhibited a slower release rate and delayed hydrolysis than Oxaliplatin alone. Cell toxicity studies using the CCK-8 assay indicated that Oxaliplatin-Naringenin had very low cytotoxicity on GES-1 cells, suggesting a higher safety profile, while Oxaliplatin-Baicalein demonstrated greater effectiveness in inhibiting SGC7901 cancer cells compared to Oxaliplatin.Yin et al. [106] employed cocrystallization to enhance the efficacy of Lobaplatin, successfully creating 5 cocrystals with various flavonoids, comprising quercetin, myricetin, fisetin, naringenin and luteolin. In comparison with pure Lobaplatin the cocrystals exhibited poorer solubility, delayed releasing and prolonged hydrolysis. The antitumor activity of the co-crystals was using the CCK-8 assay, revealing that the Lobaplatin co-crystals with Luteolin monohydrate, Myricetin monohydrate and Fisetin monohydrate demonstrated superior performance compared to Lobaplatin alone. Their results suggest that cocrystals could offer a promising approach to addressing some limitations of the parent drug.Xiao et al. [107] developed Metamitron cocrystals with Cinnamic acid, Naringenin and Baicalein. Their study found that, in comparison to purified Metamitron, the dissolution percentage cocrystal of the Metamitron-Naringenin (98.30%) and Metamitron-Baicalein (96.28%) were significantly reduced. Similarly, the soluble content of Metamitron-Naringenin and Metamitron-Baicalein reduced by 95.49% and 96.21% in each case. These cocrystals also demonstrated an extended period of action than pure Metamitron. The research explored the molecular mechanisms underlying the sustained-release effects of these cocrystals, highlighting that cocrystal formulation might be an efficient technique for achieving controlled-release properties and reducing eco-friendly impact for extremely water-soluble pesticides.Zhang et al. [108] formulated Naringenin nanocrystals to enhance its anti-rheumatoid arthritis activity. By using a planetary ball mill and wet milling with Poloxamer-407, they successfully formulated Naringenin into nanocrystals (NCs). These Naringenin-NCs demonstrated improved dissolution, increased cellular uptake and enhanced transcellular diffusion compared to bulk Naringenin. When administered orally, the Naringenin-NCs significantly increased bioavailability in rats. Furthermore, the Naringenin-NCs effectively reduced inflammation and synovial damage in collagen-induced arthritic rats, leading to better treatment outcomes for rheumatoid arthritis. Their findings suggest that Naringenin-NCs offer a promising approach for treating rheumatoid arthritis.Cui et al. [109] prepared Naringenin cocrystals by

solution crystallization technique to enhance its bioavailability and anti-hyperlipidemia effects. They successfully created several Naringenin cocrystals with different coformers, including Nicotinamide, Isonicotinamide, Caffeine, Betaine and L-proline. The cocrystal development was confirmed by DSC, XRD, NMR and FTIR. These cocrystals dramatically increased Naringenin's solubility and dissolving rate. Naringenin cocrystals with L-proline and Betaine provided considerably better oral absorption than pure Naringenin ($p < 0.05$). The C_{max} of Naringenin-L-proline was 2.00 times higher and Naringenin-Betaine cocrystals was 3.35 times higher and the AUC was 2.39 times and 4.91 times higher, in comparison with pure Naringenin in rats. Additionally, the Naringenin-Betaine cocrystals resulted in significantly increased drug distribution in the liver and demonstrated enhanced anti-hyperlipidemia action in mouse model. Their results reveal that cocrystal development is a potential technique for increasing Naringenin's absorption for hyperlipidemia treatment.Lee et al. [110] formulated a cocrystal between Naringenin and Carbamazepine, focusing on the interactions between resorcinol and urea functional groups. At a 1:1 stoichiometric ratio, Naringenin successfully formed a cocrystal with Carbamazepine. The cocrystal's stability appears to be derived from hydrogen bonds connecting Naringenin's resorcinol group and Carbamazepine's urea group. The co-crystal melting point was found to be 262°C, which is greater than either Carbamazepine or Naringenin alone, indicating improved stability. This enhanced stability was further supported by the cocrystal's increased water stability, lasting over 30 days at 93% relative humidity. Their study suggests that using natural flavonoids in cocrystallization could enhance the commercial viability of active pharmaceutical ingredient (API) cocrystals.Zhou et al. [111] conducted a study on the structure and *in vitro/in vivo* performance of a 1:1 Carbamazepine-Naringenin cocrystal. This newly formed cocrystal was characterized using various techniques, including XRD, NMR, FTIR and solid-state fluorescence. Notably, the Carbamazepine-Naringenin cocrystal exhibited a higher endothermic onset compared to the Carbamazepine and Naringenin as observed in DSC study. Additionally, the fluorescence intensity of the cocrystal was significantly lower than that of Carbamazepine. The study also included an *in vitro* and *in vivo* evaluation of how Naringenin affects Carbamazepine. Carbamazepine-Naringenin cocrystal in water solubility decreased to 7.2 ± 0.6 μg/mL, compared to 97.2 ± 1.5 μg/mL for Carbamazepine alone. The intrinsic dissolution rate (IDR) values for Carbamazepine and the cocrystal were 0.042 and 0.016 mg/cm²/min, respectively. Carbamazepine displayed a single absorption peak in plasma concentration-time curves, the cocrystal exhibited two peaks. The cocrystal also showed a lower peak absorption (C_{max} = 491.3 ± 97.6 ng/mL) and a lengthier elimination half-life ($t_{1/2}$ = 8.5 ± 1.0 h) compared to Carbamazepine alone (Cmax = 5258.1 ± 904.2 ng/mL, $t_{1/2}$ = 0.7 ± 0.2 h). These findings indicate that the Carbamazepine-Naringenin cocrystal exhibits different *in vitro* and *in vivo* behaviors compared to pure Carbamazepine.Luo et al.[112] conducted co-crystallization experiments to enhance Naringenin solubility, resulting in the creation of four new Naringenin co-crystals (Naringenin–Isonicotinamide, Naringenin–Picolinic acid, and two forms of Naringenin–Betaine). These co-crystals were thoroughly analyzed using various methods, including SCXRD, NMR (both liquid and solid-state), FTIR, and DSC. Dissolution tests showed that all four co-crystals had better apparent solubility and IDRs compared to pure Naringenin (Table 5).

Table 5 Nanosuspensions of Naringenin

Naringenin concentration	Method	Suspending agent	Ref
40 mg	Miniaturized media-milling method	Tocopheryl polyethylene glycol 1000 succinate (TPGS)	[113, 114]
30 mg	Sonoprecipitation method	Polyvinyl pyrrolidone (PVP K90)	[115, 116]
10-50 mg	Sonoprecipitation Method	PVP	[117]
7.5 mg	Precipitation-ultrasonication method	D-α- TPGS, sodium lauryl sulphate, poly ethylene glycol 4000, polysorbate 80.	[118]

Naringenin concentration	Method	Suspending agent	Ref
		sodium cholate and poloxamer-188	
2% w/v	Premilling and subsequent high-pressure homogenization method	HPMC and sodium dodecyl sulfate	[119]
50 mg/kg	High-pressure homogenization	D-α- TPGS	[120]
50, 100 and 200 mg/kg	High-pressure homogenization	D-α- TPGS	[121]
20 mg/kg	High-pressure homogenization	Soya lecithin and TPGS	[122]

CHALLENGES WITH INTEGRATED CO-CRYSTAL AND NANOTECHNOLOGY METHODS AND THEIR COUNTER MEASURES

1. Enhanced solubility: Achieving the desired solubility improvements can be inconsistent due to variations in co-crystal formation [123].
Countermeasure: Using ideal screening methods to identify optimal co-formers that consistently enhance solubility and conduct thorough characterization of co-crystals to ensure reproducibility [124].
2. Stability improvement: Co-crystals may be prone to instability under certain environmental conditions (e.g., humidity, temperature).
Countermeasure: Employment of protective coatings or encapsulation methods to enhance the stability of co-crystal formulations against environmental factors [125].
3. Controlled release profiles: Achieving consistent release rates can be difficult due to the variable interactions between the drug, co-crystal and formulation matrix.
Countermeasure: Utilization of advanced polymeric matrices or lipid-based systems designed for sustained release, allowing for more predictable release kinetics [126].
4. Particle size optimization: Maintaining uniform particle size in nanosuspensions can be challenging due to aggregation or sedimentation [127].
Countermeasure: Implementation of effective stabilization techniques, such as surfactants and polymers and utilize high shear mixing or homogenization to achieve and maintain desired particle sizes [128].
5. Targeted delivery: Targeted delivery nanosuspension systems can lead to off-target effects if not properly designed [129].
Countermeasure: Usage of specific targeting ligands or antibodies in nanosuspension formulation design and conduct *in vitro* and *in vivo* studies to validate targeting efficiency and specificity [130].
6. Additives selection: Selecting inappropriate excipients may lead to instability or reduced efficacy of the co-crystal-nanosuspension formulation [131].
Countermeasure: Conduct compatibility studies to screen for potential interactions between the drug, co-crystal and excipients, ensuring optimal formulation performance. These points emphasize the importance of addressing challenges in the formulation of integrated co-crystals and nanotechnology to develop effective, stable and scalable drug delivery systems [132].

CONCLUSION

Pharmaceutical co-crystallization offers a transformative approach to overcoming the challenges posed by poorly water-soluble APIs. By improving solubility, dissolution rates, and stability, co-crystals enhance the bioavailability and therapeutic efficacy of drugs, providing a promising solution to the limitations of conventional formulations. The growing interest in co-crystals within the pharmaceutical industry reflects their potential to optimize drug properties and expand the range of effective treatments. As

research continues to advance, co-crystals are likely to play a crucial role in the future of drug development, offering new opportunities for improving patient outcomes.

Moreover, the integration of co-crystal technology with nanosuspensions can create a synergistic effect, where the enhanced dissolution and stability of co-crystals are further improved by the reduced particle size and increased surface area provided by nanosuspensions. This combined approach has the potential to significantly enhance the bioavailability and therapeutic efficacy of challenging APIs like naringenin. The formation of Naringenin co-crystals with suitable co-formers significantly improved the solubility, permeability, and bioavailability of Naringenin, overcoming its inherent biopharmaceutical challenges. This approach represents a promising strategy to enhance the therapeutic potential of Naringenin, making it more effective for clinical applications. The co-crystals exhibited superior PK profiles compared to pure Naringenin, highlighting their potential for further development as a formulation strategy in drug delivery systems.

CONFLICT OF INTEREST

The authors verify that there are no conflicts of interest within this review article and they are not financially connected to any organization or entity with a financial stake in the subject matter discussed in this manuscript.

REFERENCES

(1) Naqvi, A.; Ahmad, M.; Minhas, M. U.; Khan, K. U.; Batool, F.; Rizwan, A. Preparation and Evaluation of Pharmaceutical Co-Crystals for Solubility Enhancement of Atorvastatin Calcium. *Polym. Bull.* 2020, *77* (12), 6191–6211. https://doi.org/10.1007/s00289-019-02997-4.

(2) Ngilirabanga, J. B.; Samsodien, H. Pharmaceutical Co-Crystal: An Alternative Strategy for Enhanced Physicochemical Properties and Drug Synergy. *Nano Select* 2021, *2* (3), 512–526. https://doi.org/10.1002/nano.202000201.

(3) Chi Lip Kwok, P.; Chan, H.-K. Nanotechnology versus Other Techniques in Improving Drug Dissolution. *Curr. Pharm. Des.* 2014, *20* (3), 474–482.

(4) Kiyonga, E. M.; Kekani, L. N.; Chidziwa, T. V.; Kahwenga, K. D.; Bronkhorst, E.; Milne, M.; Poka, M. S.; Mokhele, S.; Demana, P. H.; Witika, B. A. Nano- and Crystal Engineering Approaches in the Development of Therapeutic Agents for Neoplastic Diseases. *Crystals* 2022, *12* (7), 926. https://doi.org/10.3390/cryst12070926.

(5) Kale, D. P.; Zode, S. S.; Bansal, A. K. Challenges in Translational Development of Pharmaceutical Cocrystals. *Journal of Pharmaceutical Sciences* 2017, *106* (2), 457–470. https://doi.org/10.1016/j.xphs.2016.10.021.

(6) Kendall, T. *Co-crystallization in drug development Exploring the benefits of co-crystals.* Drug Discovery Today. http://www.drugdiscoverytoday.com/view/47964/co-crystallization-in-drug-development-exploring-the-benefits-of-co-crystals/ (accessed 2024-08-04).

(7) Yadav, A. V.; Shete, A. S.; Dabke, A. P.; Kulkarni, P. V.; Sakhare, S. S. Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients. *Indian J Pharm Sci* 2009, *71* (4), 359–370. https://doi.org/10.4103/0250-474X.57283.

(8) Xie, Y.; Zhou, J.; Zhang, B.; Zhang, L.; Yang, D.; Yang, S.; Fang, L.; Lu, Y.; Du, G. Quality Control of Naringenin-Carbamazepine Drug-Drug Cocrystal: Quantitative Analytical Method Construction of ATR-FTIR and Raman Combined with Chemometrics. *Microchemical Journal* 2024, *202*, 110774. https://doi.org/10.1016/j.microc.2024.110774.

(9) Karimi-Jafari, M.; Padrela, L.; Walker, G. M.; Croker, D. M. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications. *Crystal Growth & Design* 2018, *18* (10), 6370–6387. https://doi.org/10.1021/acs.cgd.8b00933.

(10)Izutsu, K.; Koide, T.; Takata, N.; Ikeda, Y.; Ono, M.; Inoue, M.; Fukami, T.; Yonemochi, E. Characterization and Quality Control of Pharmaceutical Cocrystals. *Chemical and Pharmaceutical Bulletin* 2016, *64* (10), 1421–1430. https://doi.org/10.1248/cpb.c16-00233.

(11)Chettri, A.; Subba, A.; Singh, G. P.; Bag, P. P. Pharmaceutical Co-Crystals: A Green Way to Enhance Drug Stability and Solubility for Improved Therapeutic Efficacy. *Journal of Pharmacy and Pharmacology* 2024, *76* (1), 1–12. https://doi.org/10.1093/jpp/rgad097.

(12)Pandey, N. K.; Sehal, H. R.; Garg, V.; Gaur, T.; Kumar, B.; Singh, S. K.; Gulati, M.; Gowthamarajan, K.; Bawa, P.; Rajesh, S. Y.; Sharma, P.; Narang, R. Stable Co-Crystals of Glipizide with Enhanced Dissolution Profiles: Preparation and Characterization. *AAPS PharmSciTech* 2017, *18* (7), 2454–2465. https://doi.org/10.1208/s12249-017-0727-z.

(13)Shi, X.; Wang, C.; Chen, Q.; Shen, S.; Song, S.; Zhou, X. Improving Physicochemical Properties of Ibrutinib with Cocrystal Strategy Based on Structures and Natures of the Carboxylic Acid Co-Formers. *Journal of Drug Delivery Science and Technology* 2021, *63*, 102554. https://doi.org/10.1016/j.jddst.2021.102554.
(14)Faculty of Chemical & Natural Resources Engineering; Rahman, F. A.; Rahim, S. A.; Chou, C. T.; Low, S. H.; Ramle, N. A. Carbamazepine-Fumaric Acid and Carbamazepine-Succinic Acid Co-Crystal Screening Using Solution Based Method. *IJCEA* 2017, *8* (2), 136–140. https://doi.org/10.18178/ijcea.2017.8.2.645.
(15)Shikhar, A.; Bommana, M. M.; Gupta, S. S.; Squillante, E. Formulation Development of Carbamazepine–Nicotinamide Co-Crystals Complexed with γ-Cyclodextrin Using Supercritical Fluid Process. *The Journal of Supercritical Fluids* 2011, *55* (3), 1070–1078. https://doi.org/10.1016/j.supflu.2010.09.009.
(16)Du, J. J.; Stanton, S. A.; Fakih, S.; Hawkins, B. A.; Williams, P. A.; Groundwater, P. W.; Overgaard, J.; Platts, J. A.; Hibbs, D. E. Exploring the Solubility of the Carbamazepine-Saccharin Cocrystal: A Charge Density Study. *Crystal Growth and Design* 2021, *21* (8), 4259–4275. https://doi.org/10.1021/acs.cgd.8b01111.
(17)Varma, A.; Laxmi, P.; Pai, A.; Pai, G.; Sg, V.; Badamane Sathyanarayana, M. Designing of Stable Co-Crystals of Zoledronic Acid Using Suitable Coformers. *Chemical and Pharmaceutical Bulletin* 2019, *67* (8), 816–823. https://doi.org/10.1248/cpb.c19-00202.
(18)Thomas, J.; Nayak, U.; P.C, J.; Koteshwara, K. Design and Characterization of Valsartan Co-Crystals to Improve Its Aqueous Solubility and Dissolution Behavior. *Research Journal of Pharmacy and Technology* 2017, *10*, 26. https://doi.org/10.5958/0974-360X.2017.00007.5.
(19)Peach, A. A.; Holmes, S. T.; MacGillivray, L. R.; Schurko, R. W. The Formation and Stability of Fluoxetine HCl Cocrystals Investigated by Multicomponent Milling. *CrystEngComm* 2023, *25* (2), 213–224. https://doi.org/10.1039/D2CE01341J.
(20)Guinet, Y.; Paccou, L.; Hédoux, A. Analysis of Co-Crystallization Mechanism of Theophylline and Citric Acid from Raman Investigations in Pseudo Polymorphic Forms Obtained by Different Synthesis Methods. *Molecules* 2023, *28* (4), 1605. https://doi.org/10.3390/molecules28041605.
(21)Qi, M.-H.; Li, H.; Zhu, B.; Hong, M.; Ren, G.-B. Cocrystals of Oxymatrine: Reducing Hygroscopicity and Affecting the Dissolution Rate. *Crystal Growth & Design* 2021, *21* (7), 3874–3888. https://doi.org/10.1021/acs.cgd.1c00205.
(22)Ren, Z.; Chen, X.; Yu, G.; Wang, Y.; Chen, B.; Zhou, Z. Molecular Simulation Studies on the Design of Energetic Ammonium Dinitramide Co-Crystals for Tuning Hygroscopicity. *CrystEngComm* 2020, *22* (31), 5237–5244. https://doi.org/10.1039/D0CE00602E.
(23)Watanabe, T.; Ito, M.; Suzuki, H.; Terada, K.; Noguchi, S. Reduced Deliquescency of Isosorbide by Cocrystallization and Mechanisms for Hygroscopicity. *International Journal of Pharmaceutics* 2021, *607*, 120959. https://doi.org/10.1016/j.ijpharm.2021.120959.
(24)Huang, S.; Xue, Q.; Xu, J.; Ruan, S.; Cai, T. Simultaneously Improving the Physicochemical Properties, Dissolution Performance, and Bioavailability of Apigenin and Daidzein by Co-Crystallization with Theophylline. *Journal of Pharmaceutical Sciences* 2019, *108* (9), 2982–2993. https://doi.org/10.1016/j.xphs.2019.04.017.
(25)Liu, L.; An, Q.; Zhang, Y.; Sun, W.; Li, J.; Feng, Y.; Geng, Y.; Cheng, G. Improving the Solubility, Hygroscopicity and Permeability of Enrofloxacin by Forming 1:2 Pharmaceutical Salt Cocrystal with Neutral and Anionic Co-Existing p-Nitrobenzoic Acid. *Journal of Drug Delivery Science and Technology* 2022, *76*, 103732. https://doi.org/10.1016/j.jddst.2022.103732.
(26)Kumbhar, P.; Kolekar, K.; Khot, C.; Dabhole, S.; Salawi, A.; Sabei, F. Y.; Mohite, A.; Kole, K.; Mhatre, S.; Jha, N. K.; Manjappa, A.; Singh, S. K.; Dua, K.; Disouza, J.; Patravale, V. Co-Crystal Nanoarchitectonics as an Emerging Strategy in Attenuating Cancer: Fundamentals and Applications. *Journal of Controlled Release* 2023, *353*, 1150–1170. https://doi.org/10.1016/j.jconrel.2022.12.042.
(27)Maeno, Y.; Fukami, T.; Kawahata, M.; Yamaguchi, K.; Tagami, T.; Ozeki, T.; Suzuki, T.; Tomono, K. Novel Pharmaceutical Cocrystal Consisting of Paracetamol and Trimethylglycine, a New Promising Cocrystal Former. *International Journal of Pharmaceutics* 2014, *473* (1), 179–186. https://doi.org/10.1016/j.ijpharm.2014.07.008.
(28)Ogata, T.; Tanaka, D.; Ozeki, T. Enhancing the Solubility and Masking the Bitter Taste of Propiverine Using Crystalline Complex Formation. *Drug Development and Industrial Pharmacy* 2014, *40* (8), 1084–1091. https://doi.org/10.3109/03639045.2013.807280.
(29)PM, P. *In-Vitro* and *in-Silico* Evaluation of the Physical Stability and Solubilization Mechanisms of Naproxen-Nicotinamide Co-Crystals. Doctoral dissertation, Saint Joseph's University, 2023. https://www.proquest.com/openview/4b0f39fa0d31ec67041ca903e82f524f/1?pq-origsite=gscholar&cbl=18750&diss=y (accessed 2024-08-08).
(30)Mohite, R.; Mehta, P.; Arulmozhi, S.; Kamble, R.; Pawar, A.; Bothiraja, C. Synthesis of Fisetin Co-Crystals with Caffeine and Nicotinamide Using the Cooling Crystallization Technique: Biopharmaceutical Studies. *New J. Chem.* 2019, *43* (34), 13471–13479. https://doi.org/10.1039/C9NJ01848D.
(31)Thenge, R.; Adhao, V.; Mehetre, G.; Chopade, N.; Chinchole, P.; Popat, R.; Darakhe, R.; Deshmukh, P.; Tekade, N.; Mohite, B.; Kayande, N.; Mahajan, N.; Patel, R.; Thenge, R.; Adhao, V.; Mehetre, G.; Chopade, N.; Chinchole, P.; Popat, R.; Darakhe, R.; Deshmukh, P.; Tekade, N.; Mohite, B.; Kayande, N.; Mahajan, N.; Patel, R. Modification of Physicochemical

Properties of Active Pharmaceutical Ingredient by Pharmaceutical Co-Crystals. In *Drug Formulation Design*; IntechOpen, 2023. https://doi.org/10.5772/intechopen.110129.
(32)Miroshnyk, I.; Mirza, S.; Sandler, N. Pharmaceutical Co-Crystals–an Opportunity for Drug Product Enhancement. *Expert Opinion on Drug Delivery* 2009, *6* (4), 333–341. https://doi.org/10.1517/17425240902828304.
(33)Qiao, N.; Wang, K.; Schlindwein, W.; Davies, A.; Li, M. *In Situ* Monitoring of Carbamazepine–Nicotinamide Cocrystal Intrinsic Dissolution Behaviour. *European Journal of Pharmaceutics and Biopharmaceutics* 2013, *83* (3), 415–426. https://doi.org/10.1016/j.ejpb.2012.10.005.
(34)Shayanfar, A.; Velaga, S.; Jouyban, A. Solubility of Carbamazepine, Nicotinamide and Carbamazepine–Nicotinamide Cocrystal in Ethanol–Water Mixtures. *Fluid Phase Equilibria* 2014, *363*, 97–105. https://doi.org/10.1016/j.fluid.2013.11.024.
(35)Huang, Y.; Sun, X.; Zhou, L.; Zhang, Z.; Zhang, S.; Yin, Q. Investigation of Ternary Phase Diagrams of Carbamazepine–Nicotinamide Cocrystal in Ethanol and Ethanol/Ethyl Acetate Mixtures at 298.15 k and 313.15 k. *J Solution Chem* 2020, *49* (1), 117–132. https://doi.org/10.1007/s10953-019-00944-5.
(36)Ying, H.; Zhang, J.; Jiang, C. Preparation of Carbamazepine-Nicotinamide Cocrystal. *Open Access Library Journal* 2021, *8* (7), 1–8. https://doi.org/10.4236/oalib.1107605.
(37)Patil, S. P.; Modi, S. R.; Bansal, A. K. Generation of 1:1 Carbamazepine:Nicotinamide Cocrystals by Spray Drying. *European Journal of Pharmaceutical Sciences* 2014, *62*, 251–257. https://doi.org/10.1016/j.ejps.2014.06.001.
(38)Ray, E.; Vaghasiya, K.; Sharma, A.; Shukla, R.; Khan, R.; Kumar, A.; Verma, R. K. Autophagy-Inducing Inhalable Co-Crystal Formulation of Niclosamide-Nicotinamide for Lung Cancer Therapy. *AAPS PharmSciTech* 2020, *21* (7), 260. https://doi.org/10.1208/s12249-020-01803-z.
(39)Sopyan, I.; Fudholi, A.; Muchtaridi, M.; Sari, I. P. Simvastatin-Nicotinamide Co-Crystal: Design, Preparation and Preliminary Characterization. *Tropical Journal of Pharmaceutical Research* 2017, *16* (2), 297–303. https://doi.org/10.4314/tjpr.v16i2.6.
(40)Khan, F. M.; Ahmad, M.; Idrees, H. A. Simvastatin-Nicotinamide Co-Crystals: Formation, Pharmaceutical Characterization and *in Vivo* Profile. *Drug Design, Development and Therapy* 2020, *14*, 4303–4313. https://doi.org/10.2147/DDDT.S270742.
(41)Shewale, S.; Shete, A. S.; Doijad, R. C.; Kadam, S. S.; Patil, V. A.; Yadav, A. V. Formulation and Solid State Characterization of Nicotinamide-Based Co-Crystals of Fenofibrate. *Indian J Pharm Sci* 2015, *77* (3), 328–334.
(42)Shete, A. S.; Shah, V. V.; Bhosale, P. A.; Doijad, R. C. Fenofibrate-Nicotinamide Cocrystals: Molecular Docking Studies and Evaluation in Tablet Dosage Form. *Indian Journal of Pharmaceutical Sciences* 2022, *84* (3), 560.
(43)Shete, A. S. Solid State Characterization and Tableting Studies of Ethanol Based Cocrystals of Fenofibrate with Nicotinamide. *Indian Journal of Pharmaceutical Education and Research* 2018, *52* (1), 71–77. https://doi.org/10.5530/ijper.52.1.8.
(44)Yadav, D.; Savjani, J.; Savjani, K.; Kumar, A.; Patel, S. Pharmaceutical Co-Crystal of Antiviral Agent Efavirenz with Nicotinamide for the Enhancement of Solubility, Physicochemical Stability, and Oral Bioavailability. *AAPS PharmSciTech* 2022, *24* (1), 7. https://doi.org/10.1208/s12249-022-02467-7.
(45)Huang, Y.; Zhang, B.; Gao, Y.; Zhang, J.; Shi, L. Baicalein–Nicotinamide Cocrystal with Enhanced Solubility, Dissolution, and Oral Bioavailability. *Journal of Pharmaceutical Sciences* 2014, *103* (8), 2330–2337. https://doi.org/10.1002/jps.24048.
(46)Chaves Júnior, J. V.; dos Santos, J. A. B.; Lins, T. B.; de Araújo Batista, R. S.; de Lima Neto, S. A.; de Santana Oliveira, A.; Nogueira, F. H. A.; Gomes, A. P. B.; de Sousa, D. P.; de Souza, F. S.; Aragão, C. F. S. A New Ferulic Acid–Nicotinamide Cocrystal with Improved Solubility and Dissolution Performance. *Journal of Pharmaceutical Sciences* 2020, *109* (3), 1330–1337. https://doi.org/10.1016/j.xphs.2019.12.002.
(47)Utami, D.; Nugrahani, I.; Ibrahim, S. Formation and Characterization of Mefenamic Acid-Nicotinamide Cocrystal during Co-Milling Based on x-Ray Powder Diffraction Analysis. *J App Pharm Sci* 2016, *6*, (10), 075–081. https://doi.org/10.7324/JAPS.2016.601010.
(48)Vaksler, Ye. A.; Benedis, D.; Dyshin, A. A.; Oparin, R. D.; Correia, N. T.; Capet, F.; Shishkina, S. V.; Kiselev, M. G.; Idrissi, A. Spectroscopic Characterization of Single Co-Crystal of Mefenamic Acid and Nicotinamide Using Supercritical CO2. *Journal of Molecular Liquids* 2021, *334*, 116117. https://doi.org/10.1016/j.molliq.2021.116117.
(49)Srinivasan, P.; Almutairi, M.; Dumpa, N.; Sarabu, S.; Bandari, S.; Zhang, F.; Ashour, E.; Repka, M. A. Theophylline-Nicotinamide Pharmaceutical Co-Crystals Generated Using Hot Melt Extrusion Technology: Impact of Polymeric Carriers on Processability. *Journal of Drug Delivery Science and Technology* 2021, *61*, 102128. https://doi.org/10.1016/j.jddst.2020.102128.
(50)Al-Nimry, S. S.; Khanfar, M. S. Enhancement of the Solubility of Asenapine Maleate through the Preparation of Co-Crystals. *Current Drug Delivery* 2022, *19* (7), 788–800. https://doi.org/10.2174/1567201818666210805154345.
(51)Yuliandra, Y.; Zaini, E.; Syofyan, S.; Pratiwi, W.; Putri, L. N.; Pratiwi, Y. S.; Arifin, H. Cocrystal of Ibuprofen–Nicotinamide: Solid-State Characterization and *in Vivo* Analgesic Activity Evaluation. *Scientia Pharmaceutica* 2018, *86* (2), 23. https://doi.org/10.3390/scipharm86020023.
(52)Wang, L.; Yan, Y.; Zhang, X.; Zhou, X. Novel Pharmaceutical Cocrystal of Lenalidomide with Nicotinamide: Structural Design, Evaluation, and Thermal Phase Transition Study. *International Journal of Pharmaceutics* 2022, *613*, 121394. https://doi.org/10.1016/j.ijpharm.2021.121394.

(53)Lin, H.-L.; Zhang, G.-C.; Huang, Y.-T.; Lin, S.-Y. An Investigation of Indomethacin–Nicotinamide Cocrystal Formation Induced by Thermal Stress in the Solid or Liquid State. *Journal of Pharmaceutical Sciences* 2014, *103* (8), 2386–2395. https://doi.org/10.1002/jps.24056.
(54)Tawfeek, H. M.; Chavan, T.; Kunda, N. K. Effect of Spray Drying on Amorphization of Indomethacin Nicotinamide Cocrystals; Optimization, Characterization, and Stability Study. *AAPS PharmSciTech* 2020, *21* (5), 181. https://doi.org/10.1208/s12249-020-01732-x.
(55)Kamis, M. N. A. A.; Zaki, H. M.; Anuar, N.; Jalil, M. N. Synthesis, Characterization and Morphological Study of Nicotinamide and p-Coumaric Acid Cocrystal. *Indonesian Journal of Chemistry* 2020, *20* (3), 661–679. https://doi.org/10.22146/ijc.45530.
(56)Joshi, T. V.; Singaraju, A. B.; Shah, H. S.; Morris, K. R.; Stevens, L. L.; Haware, R. V. Structure–Mechanics and Compressibility Profile Study of Flufenamic Acid:Nicotinamide Cocrystal. *Crystal Growth & Design* 2018, *18* (10), 5853–5865. https://doi.org/10.1021/acs.cgd.8b00534.
(57)Haifen, L. I. U.; Beibei, T.; Zhengzheng, Y.; Lianhua, M. A.; Lixin, W. Comprehensive Experiments on Preparation and Characterization of Pharmaceutical Co-Crystals Based on Acetaminophen and Nicotinamide. | Experimental Technology & Management | EBSCOhost. *Experimental Technology & Management* 2022, *39* (7), 202. https://doi.org/10.16791/j.cnki.sjg.2022.07.035.
(58)AS, S.; AV, Y.; RC, D. Screening of Aceclofenac for Cocrystallization with Nicotinamide: Theoretical and Practical Perspective. *Indian Journal of Pharmaceutical Sciences* 2022, *84* (6), 1389. https://doi.org/10.36468/pharmaceutical-sciences.1037.
(59)Xiao, Y.; Jin, T.; Geng, X.; Zhu, X. Azilsartan-Nicotinamide Cocrystal: Preparation, Characterization and *in Vitro / Vivo* Evaluation. *European Journal of Pharmaceutical Sciences* 2022, *176*, 106241. https://doi.org/10.1016/j.ejps.2022.106241.
(60)Ghosh, S.; Bag, P. P.; Reddy, C. M. Co-Crystals of Sulfamethazine with Some Carboxylic Acids and Amides: Co-Former Assisted Tautomerism in an Active Pharmaceutical Ingredient and Hydrogen Bond Competition Study. *Crystal Growth & Design* 2011, *11* (8), 3489–3503. https://doi.org/10.1021/cg200334m.
(61)Sarcevica, I.; Orola, L.; Veidis, M. V.; Podjava, A.; Belyakov, S. Crystal and Molecular Structure and Stability of Isoniazid Cocrystals with Selected Carboxylic Acids. *Crystal Growth & Design* 2013, *13* (3), 1082–1090. https://doi.org/10.1021/cg301356h.
(62)Diniz, L. F.; Souza, M. S.; Carvalho, P. S.; da Silva, C. C. P.; D'Vries, R. F.; Ellena, J. Novel Isoniazid Cocrystals with Aromatic Carboxylic Acids: Crystal Engineering, Spectroscopy and Thermochemical Investigations. *Journal of Molecular Structure* 2018, *1153*, 58–68. https://doi.org/10.1016/j.molstruc.2017.09.115.
(63)Cheney, M. L.; Weyna, D. R.; Shan, N.; Hanna, M.; Wojtas, L.; Zaworotko, M. J. Supramolecular Architectures of Meloxicam Carboxylic Acid Cocrystals, a Crystal Engineering Case Study. *Crystal Growth & Design* 2010, *10* (10), 4401–4413. https://doi.org/10.1021/cg100514g.
(64)Hu, Y.; Gniado, K.; Erxleben, A.; McArdle, P. Mechanochemical Reaction of Sulfathiazole with Carboxylic Acids: Formation of a Cocrystal, a Salt, and Coamorphous Solids. *Crystal Growth & Design* 2014, *14* (2), 803–813. https://doi.org/10.1021/cg401673z.
(65)SAMANTA, R.; KANAUJIA, S.; REDDY, C. M. New Co-Crystal and Salt Form of Sulfathiazole with Carboxylic Acid and Amide. *J Chem Sci* 2014, *126* (5), 1363–1367. https://doi.org/10.1007/s12039-014-0698-5.
(66)Surov, A. O.; Voronin, A. P.; Vasilev, N. A.; Churakov, A. V.; Perlovich, G. L. Cocrystals of Fluconazole with Aromatic Carboxylic Acids: Competition between Anhydrous and Hydrated Solid Forms. *Crystal Growth & Design* 2020, *20* (2), 1218–1228. https://doi.org/10.1021/acs.cgd.9b01490.
(67)Childs, S. L.; Hardcastle, K. I. Cocrystals of Piroxicam with Carboxylic Acids. *Crystal Growth & Design* 2007, *7* (7), 1291–1304. https://doi.org/10.1021/cg060742p.
(68)Ren, B.-Y.; Dai, X.-L.; Wang, J.; Wu, C.; Lu, T.-B.; Chen, J.-M. Cocrystallization of Axitinib with Carboxylic Acids: Preparation, Crystal Structures and Dissolution Behavior. *CrystEngComm* 2021, *23* (32), 5504–5515. https://doi.org/10.1039/D1CE00620G.
(69)Przybyłek, M.; Ziółkowska, D.; Mroczyńska, K.; Cysewski, P. Propensity of Salicylamide and Ethenzamide Cocrystallization with Aromatic Carboxylic Acids. *European Journal of Pharmaceutical Sciences* 2016, *85*, 132–140. https://doi.org/10.1016/j.ejps.2016.02.010.
(70)Hossain Mithu, M. S.; Ross, S. A.; Hurt, A. P.; Douroumis, D. Effect of Mechanochemical Grinding Conditions on the Formation of Pharmaceutical Cocrystals and Co-Amorphous Solid Forms of Ketoconazole – Dicarboxylic Acid. *Journal of Drug Delivery Science and Technology* 2021, *63*, 102508. https://doi.org/10.1016/j.jddst.2021.102508.
(71)Limwikrant, W.; Nagai, A.; Hagiwara, Y.; Higashi, K.; Yamamoto, K.; Moribe, K. Formation Mechanism of a New Carbamazepine/Malonic Acid Cocrystal Polymorph. *International Journal of Pharmaceutics* 12AD, *431* (1–2), 237–240. https://doi.org/10.1016/j.ijpharm.2012.04.027.
(72)Fu, Q.; Han, Y.; Xie, Y.; Gong, N.; Guo, F. Carbamazepine Cocrystals with Several Aromatic Carboxylic Acids in Different Stoichiometries: Structures and Solid State Characterization. *Journal of Molecular Structure* 2018, *1168*, 145–152. https://doi.org/10.1016/j.molstruc.2018.04.100.

(73)Schultheiss, N.; Lorimer, K.; Wolfe, S.; Desper, J. Attempted Construction of Minoxidil: Carboxylic Acid Cocrystals; 7 Salts and 1 Cocrystal Resulted. *CrystEngComm* 2010, *12* (3), 742–749. https://doi.org/10.1039/B910136E.
(74)Shajan, D. K.; Pandey, N.; Ghosh, A.; Chanduluru, H. K.; Sanphui, P. Investigating the Effect of Emtricitabine Cocrystals with Aromatic Carboxylic Acids on Solubility and Diffusion Permeability. *Crystal Growth & Design* 2023, *23* (7), 5289–5300. https://doi.org/10.1021/acs.cgd.3c00485.
(75)Structural Characterization and Pharmaceutical Properties of Three Novel Cocrystals of Ethenzamide With Aliphatic Dicarboxylic Acids. *Journal of Pharmaceutical Sciences* 2019, *108* (4), 1476–1485. https://doi.org/10.1016/j.xphs.2018.10.060.
(76)Aitipamula, S.; Wong, A. B. H.; Chow, P. S.; Tan, R. B. H. Pharmaceutical Cocrystals of Ethenzamide: Structural, Solubility and Dissolution Studies. *CrystEngComm* 2012, *14* (24), 8515–8524. https://doi.org/10.1039/C2CE26325D.
(77)Othman, F.; Anuar, N.; Yusop, S.; Salwani, M.; Samad, N. Morphology Prediction and Dissolution Behavior of α-Succinic Acid in Ethanol Solution Using Molecular Dynamic Simulation. *Key Engineering Materials* 2019, *797*, 139–148. https://doi.org/10.4028/www.scientific.net/KEM.797.139.
(78)Singh, M.; Barua, H.; Jyothi, V. G. S. S.; Dhondale, M. R.; Nambiar, A. G.; Agrawal, A. K.; Kumar, P.; Shastri, N. R.; Kumar, D. Cocrystals by Design: A Rational Coformer Selection Approach for Tackling the API Problems. *Pharmaceutics* 2023, *15* (4), 1161. https://doi.org/10.3390/pharmaceutics15041161.
(79)Ullah, M.; Hussain, I.; Sun, C. C. The Development of Carbamazepine-Succinic Acid Cocrystal Tablet Formulations with Improved in Vitro and in Vivo Performance. *Drug Development and Industrial Pharmacy* 2016, *42* (6), 969–976. https://doi.org/10.3109/03639045.2015.1096281.
(80)Wicaksono, Y.; Setyawan, D.; Siswandono, S.; Siswoyo, T. A. Preparation and Characterization of a Novel Cocrystal of Atorvastatin Calcium with Succinic Acid Coformer. *Indonesian Journal of Chemistry* 2019, *19* (3), 660–667. https://doi.org/10.22146/ijc.35801.
(81)Fuliaş, A.; Vlase, G.; Vlase, T.; Şuta, L.-M.; Şoica, C.; Ledeţi, I. Screening and Characterization of Cocrystal Formation between Carbamazepine and Succinic Acid. *J Therm Anal Calorim* 2015, *121* (3), 1081–1086. https://doi.org/10.1007/s10973-015-4473-8.
(82)Setyawan, D.; Adyaksa, F. R.; Sari, H. L.; Paramita, D. P.; Sari, R. Cocrystal Formation of Loratadine-Succinic Acid and Its Improved Solubility. *Journal of Basic and Clinical Physiology and Pharmacology* 2021, *32* (4), 623–630. https://doi.org/10.1515/jbcpp-2020-0456.
(83)Noonan, T. J.; Chibale, K.; Bourne, S. A.; Caira, M. R. A Preformulation Co-Crystal Screening Case Study: Polymorphic Co-Crystals of an Imidazopyridazine Antimalarial Drug Lead with the Coformer Succinic Acid. *Journal of Molecular Structure* 2020, *1204*, 127561. https://doi.org/10.1016/j.molstruc.2019.127561.
(84)Issa, N.; Barnett, S. A.; Mohamed, S.; Braun, D. E.; Copley, R. C. B.; Tocher, D. A.; Price, S. L. Screening for Cocrystals of Succinic Acid and 4-Aminobenzoic Acid. *CrystEngComm* 2012, *14* (7), 2454–2464. https://doi.org/10.1039/C2CE06325E.
(85)Hasanah, U.; Fitriani, L.; Putri, V. N.; Zaini, E. Formulation and Evaluation of Orally Disintegrating Film (ODF) Containing Piperine-Succinic Acid Cocrystal. *Pharmaciana* 2023, *13* (1), 108–118. https://doi.org/10.12928/pharmaciana.v13i1.25286.
(86)Ober, C. A.; Gupta, R. B. Formation of Itraconazole–Succinic Acid Cocrystals by Gas Antisolvent Cocrystallization. *AAPS PharmSciTech* 2012, *13* (4), 1396–1406. https://doi.org/10.1208/s12249-012-9866-4.
(87)Imanto, T.; Wikantyasning, E.; Nurwaini, S.; Amalia, M.; Sambudi, N.; yub harun, N. Preparation and Solid-State Characterization of Ketoprofen-Succinic Acid-Saccharin Co-Crystal with Improved Solubility. *International Journal of Applied Pharmaceutics* 2024, *16* (1), 275–279. https://doi.org/10.22159/ijap.2024v16i1.48829.