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Nanococrystals in Pharmaceutical Development: Design, Characterization, and Applications

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ABSTRACT

Drug solubility is a fundamental challenge in pharmaceutical development, especially for oral dosage forms where poor solubility limits therapeutic effectiveness. Among the approaches explored to address this issue, cocrystals and nanocrystals have shown notable advantages in improving physicochemical properties and drug delivery. Nanococrystals, which integrate the principles of both systems, represent a promising platform with potential benefits in solubility, bioavailability, and stability. This study was designed as a systematic literature review of publications from 2015 to 2025 retrieved from PubMed, Scopus, Web of Science (WoS), and ScienceDirect. Relevant studies were analyzed thematically to provide insights into nanococrystal design, including the role of active pharmaceutical ingredients, coformers, stabilizers, and solvents. Fabrication methods such as antisolvent precipitation, wet milling, high pressure homogenization, and spray flash evaporation were reviewed alongside characterization techniques including X-ray diffraction, thermal analysis, spectroscopy, and microscopy. Applications of nanococrystals consistently demonstrate significant improvements in solubility, dissolution rate, and oral bioavailability compared to conventional forms, confirming their potential as an advanced drug delivery strategy for future pharmaceutical development.

Keywords: Nanococrystal, crystal, solubility, bioavailability, stability

Introduction

Solubility remains a fundamental challenge in pharmaceutical development, particularly for oral dosage forms. Since drugs must dissolve prior to diffusion and absorption, poor solubility can significantly limit therapeutic effectiveness. This issue has become increasingly critical with the growing trend of new drug candidates belonging to Biopharmaceutics Classification System (BCS) classes II and IV (Ainurofiq et al., 2021; Samineni et al., 2022). Over the years, various strategies have

been explored, ranging from physical approaches such as particle size reduction (micronization and nanonization) to chemical modifications including salt formation, complexation, and cocrystallization. carrier-based techniques, such as solid dispersions, micelles, and liposomes, have also been investigated (Grifasi et al., 2015; Lin et al., 2017; Lee, 2020; Susanto et al., 2024; Chhatbar et al., 2025).

Cocrystals are particularly attractive because they not only improve solubility but also enhance the physical properties of active pharmaceutical ingredients (APIs) (Sakhiya & Borkhataria, 2024). For instance, telmisartan–oxalic acid cocrystals have been shown to reduce lamination and capping during compression (Ratih et al., 2020). Nevertheless, cocrystal formation requires highly specific non-covalent interactions between the drug and coformer, such as hydrogen bonding or other weak intermolecular forces. This structural specificity often limits optimization. In some cases, solubility improvements have been modest, such as a 1.5-fold increase observed in etoricoxib (Y. Wang et al., 2022) and metformin HCl cocrystals (Bhatt et al., 2020). These limitations highlight the need for combining multiple solubility enhancement approaches.

Nanocrystals, defined as crystals in the nanometer range (<800 nm), represent another promising strategy. Several nanocrystal-based formulations have already reached the market, including Emend® and Tricor® (Jakubowska, 2024; Rossier et al., 2024). By increasing the surface area of APIs, nanocrystals significantly improve solubility and bioavailability. For example, nintedanib and cannabidiol demonstrated marked bioavailability enhancement when formulated as nanocrystals (Fu et al., 2022; Zhu et al., 2022). Given their complementary mechanisms, combining cocrystals and nanocrystals could provide synergistic benefits, though research in this area remains limited and technically challenging.

Nanococrystals thus offer a promising platform with potential advantages including improved solubility, bioavailability, stability, and physicochemical properties. However, their development presents challenges across preformulation, formulation design, manufacturing, and evaluation stages. Consequently, a comprehensive review of nanococrystal research is essential to guide future design and development toward clinically viable formulations.

Methodology

Research Design

This study was designed as a systematic literature review to obtain a comprehensive overview of pharmaceutical nanococrystal research. The review focused on trends, methodologies, and applications reported over the past decade.

Data Sources

Relevant literature was retrieved from reputable international databases, including Google Scholar, PubMed, ScienceDirect, and SpringerLink. The search was restricted to publications between 2015 and 2025 to ensure the inclusion of recent advances.

Data Collection Method

A keyword-based strategy was employed, using combinations of the terms "nanocrystal," "nanococrystal," "cocrystal," "nanocrystalline drug delivery," and "pharmaceutical nanococrystal." Retrieved records were exported and screened to remove duplicates prior to analysis.

Procedure

The selection process was conducted in multiple stages. Titles and abstracts were first reviewed to assess initial relevance. Articles that passed this stage underwent full-text evaluation to confirm compliance with inclusion and exclusion criteria. Extracted data from eligible publications were organized thematically into four categories: (i) nanococrystal synthesis and engineering strategies, (ii) improvements in drug bioavailability, (iii) physicochemical characterization techniques, and (iv) challenges and future perspectives.

Criteria

Inclusion criteria consisted of English-language original research articles that specifically investigated nanococrystal preparation methods, physicochemical characterization, stability, bioavailability, or clinical applications. Exclusion criteria included review article and studies addressing nanoparticles without a clear focus on nanococrystals.

Result and Discussion

1. General Overview

The concept of cocrystals was first introduced in 1844 by Friedrich Wöhler in his study of quinhydrone, a crystalline complex formed between quinone and hydroquinone. Since then, cocrystal research has expanded significantly (Saraf et al., 2022). In 2011, the US Food and Drug Administration (USFDA) issued its first draft guidance on pharmaceutical cocrystals, later updated in 2018. The USFDA defines cocrystals as crystalline materials composed of two or more molecules within a single crystal lattice. Importantly, they are classified as drug product intermediates intended to improve the efficiency of active pharmaceutical ingredients (APIs) without altering their pharmacological activity (FDA, 2018).

The European Medicines Agency (EMA) provides a more specific definition, requiring that the interactions involved be non-ionic. According to the EMA, cocrystals are homogeneous crystalline structures consisting of two or more components in a defined stoichiometric ratio, where the crystal assembly is not based on ionic bonding (European Medicine Agency, 2015). Both regulatory agencies agree that cocrystals represent a single crystalline phase comprising at least two components—typically an API and a coformer—held together through non-ionic interactions such as hydrogen bonding, π–π stacking, or van der Waals forces (Samuel Rigilin et al., 2022).

Cocrystals are known to modify both physicochemical and mechanical properties of APIs. Such modifications include changes in crystal system, crystal habit, and crystal size, which in turn affect stability, solubility, hygroscopicity, and tabletability. For example, (Yan et al., 2022) reported that the formation of a

metformin hydrochloride–citric acid cocrystal improved both mechanical performance and physicochemical characteristics.

Building on the discussion of cocrystals, nanocrystals are defined as crystalline drug substances in the nanometer range, often formulated with stabilizers to ensure stability within dosage forms (Pardhi et al., 2019). Over the past decades, nanocrystal research has advanced rapidly due to their notable advantages, such as enhanced solubility and bioavailability (Kunjir et al., 2025), as well as applications in modified drug release (Sreeharsha et al., 2022; Zhu et al., 2022). Nanocrystals are generally prepared using principles common to nanotechnology, either through top-down approaches (Stahr et al., 2021), bottom-up techniques (Castillo Henríquez et al., 2024), or combinations of both (Sartori et al., 2022). Their success is further reflected by several active pharmaceutical ingredients (APIs) that have reached commercialization, such as aprepitant, marketed as Emend® for antiemetic therapy (Jakubowska, 2024; Rossier et al., 2024).

More recently, efforts have focused on combining cocrystal and nanocrystal technologies to produce nanococrystals, a term that simply refers to cocrystals at the nanoscale. By reducing particle size, nanococrystals can further optimize drug solubility and absorption. Nanococrystals offer multiple advantages, including improved solubility compared to cocrystals, better physical stability, reduced pH dependency of solubility, and lower hygroscopicity compared to nanocrystals. For instance, the nanococrystal formation of furosemide not only show great improvement in dissolution and solubilization study but also in the chemical stability compared to single nanocrystalline (Karashima et al., 2016). However, deeper understanding should possessed to overcome their significant challenges due to its complex nature.

2. Design Principles of Nanococrystals

Preformulation is a critical step in the development of any pharmaceutical product, as an appropriate formulation serves as the foundation for achieving the desired quality of the dosage form. Nanococrystal formulation can be viewed as a combination of cocrystal and nanocrystal strategies, typically involving three components: the API, a coformer, and a stabilizer.

2.1. Active Pharmaceutical Ingredients

The physicochemical properties of an active pharmaceutical ingredient (API) are fundamental parameters that must always be considered in the development of any dosage form. The chemical structure of the API plays a key role in nanococrystal formation. Cocrystal formation arises from interactions between supramolecular synthons involving non-covalent bond donors and acceptors. Among these, hydrogen bonding is the most common interaction in cocrystal assembly. The presence of specific functional groups—such as halogens as bond donors, or carboxylate, amine, amide, and hydroxyl groups as bond acceptors—thus serves as a critical indicator for nanococrystal formation (Bhandari et al., 2020). Unlike salts, where ionic bonds predominate, cocrystals rely on non-covalent, non-ionic interactions. Therefore, evaluating ionization tendencies through pKa and ΔpKa values is essential for distinguishing between salt and cocrystal formation A more detailed discussion of

ΔpKa calculations is presented in the subsequent subsection on coformers (Z. Wang et al., 2023).

Nanoparticle formulation often requires considerable energy input, which raises concerns regarding API stability. For instance, milling may not be a suitable approach for APIs that are sensitive to heat as the longer milling time cause increase of temperature (Witika et al., 2020). Similarly, when nanoformulation methods involve solvents, such as anti-solvent precipitation, the solubility of the API becomes a decisive parameter in selecting an appropriate solvent system (Thakor et al., 2020).

2.2. Coformer

Coformers are components that form cocrystals by interacting within a single crystal lattice through non-covalent bonds. They play a crucial role in modifying the physicochemical properties and stability of the resulting cocrystals or nanococrystals. As supporting materials, coformers must be non-toxic; therefore, they are preferably selected from GRAS (Generally Recognized as Safe) substances. These materials are those that have been empirically used either through scientific procedures or in food prior to 1958. They are considered safe for humans when present in certain quantities. Accordingly, the concentration of the coformer must also comply with the acceptable daily intake (ADI) (Singh et al., 2023).

Beyond safety considerations, coformers must also possess physicochemical compatibility to form cocrystals with the target API. Several approaches can be employed to identify suitable coformers. Literature studies represent the simplest method for coformer selection. Cocrystal formation requires facilitation through non-covalent interactions between the API and the coformer. The presence of supramolecular synthons capable of acting as donors or acceptors of non-covalent bonds enables intermolecular interactions. These supramolecular synthons may be classified as homosynthons or heterosynthons. For example, in the formation of 1:1 urea–succinic acid nanococrystals, supramolecular synthons played a key role. The cocrystal was formed based on heterosynthon interactions between the $-NH_2$ group of urea and the two –OH groups of succinic acid, as well as homosynthon interactions between the –OH group of urea and the –OH group of succinic acid (Q. Yu et al., 2021).

The ΔpKa calculation method is among the most widely used approaches, offering higher success rates compared to literature studies while maintaining simplicity. The pKa value of a material indicates its degree of ionization. A $\Delta pKa < -1$ suggests a tendency for cocrystal formation, while a $\Delta pKa > 4$ suggests salt formation. A ΔpKa between 1 and 4 may indicate the possibility of forming either cocrystals or salts, which requires further confirmation using other analytical techniques (Z. Wang et al., 2023). Computational applications have also been increasingly employed in nanococrystal development. For instance, COSMO-RS software has been used to identify suitable coformers for the formation of carvedilol nanococrystals (Mohammady et al., 2021).

The solubility of the coformer is a critical factor, particularly when solvent-based methods are employed. In the preparation of furosemide nanococrystals using wet milling, some cocrystals formed with coformers that have much higher solubility than the API, such as urea and nicotinamide, were found to undergo dissociation. In

contrast, coformers such as caffeine and cytosine were able to maintain their cocrystal structure even under high-energy processing. Bond strength, which often correlates with a high melting point, is also a reliable indicator for selecting suitable API and coformer combinations in nanococrystal formation (Karashima et al., 2016).

In addition to playing a critical role during processing, coformers also contribute to defining the physicochemical properties of the resulting nanococrystals. Ezetimibe exhibited the highest solubility when formulated as nanococrystals with maleic acid as the coformer. Maleic acid has a relatively high dipole moment, which facilitates intermolecular interactions with water molecules. It is further suggested that the strong hydrogen bonding capacity of maleic acid with ezetimibe enhances the ability of the cocrystal to interact with water molecules (Bhandari et al., 2020).

In general, the most commonly used coformers are carboxylate derivatives such as oxalic acid, citric acid, and succinic acid. In addition, nicotinamide and saccharin are frequently utilized as coformers due to their hydrogen bond donor and acceptor functionalities. The use of zwitterions as coformers has also gained increasing attention, as demonstrated in the formation of diclofenac–proline and 5-fluorouracil–proline nanococrystals (Nugrahani & Auli, 2020; Y.-M. Yu et al., 2022).

Although coformers often do not exhibit pharmacological effects, several studies have explored the use of pharmacologically active coformers in nanococrystal formation. This approach not only enhances physicochemical properties but also directly improves pharmacological activity. For example, in the development of cytarabine–uracil nanococrystals, uracil was found to increase the uptake of cytarabine by tumor cells (Y.-M. Yu et al., 2023). A similar strategy was applied in the formation of paclitaxel–disulfiram nanococrystals, where disulfiram acted as a multidrug resistance modulator (Mohammad et al., 2018). Both strategies demonstrated significant improvements in therapeutic activity.

In summary, coformers serve as indispensable components in the design of nanococrystals, influencing not only their formation but also their physicochemical stability, solubility, and, in some cases, pharmacological performance. Careful selection based on safety, compatibility, ionization potential, solubility, and bonding capacity is therefore essential to ensure successful nanococrystal development. As research advances, the use of both traditional GRAS substances and pharmacologically active coformers highlights the growing potential of coformer engineering as a strategy to optimize drug delivery and therapeutic outcomes.

2.3. Stabilizer

Nanoparticulate systems possess high entropy, which leads to inherent instability. The Gibbs free energy of the system is elevated due to the reduction in particle size. A natural stabilization mechanism that frequently occurs is the formation of aggregates or agglomerates as a means of increasing particle size. Therefore, the presence of stabilizers is a critical factor in the development of nanosized formulations. In general, stabilizers can be categorized into two types based on their mechanism of action. The first is ionic stabilizers, which act as counterions of the drug itself. When adsorbed onto the drug particle surface, ionic stabilizers generate electrostatic repulsion between particles, thereby preventing aggregation (Kojima et al., 2018). Several formulations have successfully employed

this method, such as the formation of lamivudine–zidovudine nanococrystals, which produced particles of 271.0 ± 92.0 nm with a polydispersity index of 0.467 ± 0.073 and a zeta potential of –41.9 ± 3.94 mV using SDS as the stabilizer (Witika et al., 2020).

However, ionic stabilizers are often unstable in the presence of electrolytes, which can increase the risk of instability during dissolution. Consequently, steric stabilizers are generally preferred. These stabilizers function by providing steric hindrance between drug particles, preventing close interactions and reducing the likelihood of aggregation or agglomeration (Z. Huang et al., 2022). Steric stabilizers may consist of surfactants or non-surfactant polymers. The use of non-surfactant polymers is relatively limited and has often shown suboptimal results, as demonstrated in the preparation of naproxen nanococrystals, which displayed a broad particle size distribution (Santos et al., 2022). Nevertheless, PVPA-64 has shown superior inhibition of crystal growth compared to other polymeric surfactants such as poloxamer 407 and Span 80, producing particles as small as 308.15 nm, whereas other stabilizers remained in the micrometer range (Thakor et al., 2020).

A combination of ionic and steric stabilizers is frequently employed to improve formulation performance. For instance, Karashima et al. (2016) used SDS together with HPMC as stabilizers. Although the SDS concentration is expected to dominate the negative charge for zeta potential, the results showed dependency on HPMC concentration. The excess HPMC concentration may inhibit the incorporation of SDS into nanococrystals through steric repulsion, ultimately resulting in insufficient nanonization of the nanosuspension (Mohammady et al., 2021).

The type of stabilizer may also influence morphology, as observed in naproxen–nicotinamide nanococrystals. Span 85 produced rod-shaped crystals, whereas Tween 85 generated plate-shaped crystals, indicating that stabilizers can significantly affect crystallization pathways and crystal morphology (Santos et al., 2022).

The concentration of stabilizers must be carefully optimized. At insufficient concentrations, stabilizers cannot adequately cover particle surfaces, resulting in poor stabilization. A well-stabilized surface leads to smaller particle sizes, as observed in the preparation of carvedilol nanococrystals, where increasing concentrations of poloxamer reduced particle size within a certain range. However, excessively high stabilizer concentrations produced larger particles, which may result from increased viscosity hindering dispersion. Furthermore, Ostwald ripening can also contribute to particle size growth. This phenomenon was observed with SDS, a surfactant that enhances drug solubility. Increased solubility, in turn, can accelerate Ostwald ripening. A similar effect may also occur with the addition of polymeric layers on particle surfaces, which further enhance solubility (Mohammady et al., 2021).

In conclusion, stabilizers are indispensable for ensuring the stability, size control, and morphological integrity of nanococrystals. Both ionic and steric mechanisms provide distinct advantages, and their combination often yields superior outcomes. However, the choice of stabilizer type, concentration, and compatibility with the API critically determines formulation success. Optimizing these parameters not only prevents aggregation and Ostwald ripening but also enhances the reproducibility and performance of nanococrystal-based drug delivery systems.

2.4. Solvent

Several methods for preparing nanococrystals, such as wet milling, solvent evaporation, and antisolvent techniques, involve the use of solvents during processing. One of the major challenges in nanococrystal preparation is the selection of an appropriate solvent and antisolvent. The chosen solvent must provide sufficient solubility for both the drug and the coformer to allow adequate interaction during crystallization. When a large amount of organic solvent is required to dissolve the components, longer evaporation times are needed, resulting in prolonged contact between particles and the solvent, which may increase particle size (Thakor et al., 2020).

Solubility determination can be carried out either empirically or computationally. An empirical approach was used in the preparation of phenazopyridine–phthalimide nanococrystals, which showed enhanced in vitro release rates and increased bioavailability (Y. Huang et al., 2017). Computational tools, such as the COSMO-RS (Conductor-like Screening Model for Real Solvents) software, have also been employed to design more efficient processes, as demonstrated by Mohammady et al. (2021).

In anti-solvent method, it is more challenging as we should select solvents and antisolvents with markedly different solubility for the drug and coformer may cause precipitation of one component without co-crystal formation. For example, when water was used as an antisolvent, carbamazepine precipitated alone without forming a cocrystal due to the high solubility of nicotinamide in water (Thakor et al., 2020).

The solvent-to-antisolvent ratio also strongly influences particle size, as shown in the preparation of carvedilol nanococrystals. An increased water-to-acetone ratio significantly reduced particle size. However, this effect was dependent on the API concentration: at high API concentrations, particle size decreased with a higher ratio, whereas at low concentrations, the same increase in ratio led to particle size enlargement. Meanwhile for solvent evaporation methods, solvents with low boiling points are preferable, as they shorten the recrystallization process and reduce residual solvent effects (Nugrahani & Auli, 2020).

In addition, solvents affect the solubility of the resulting nanococrystals. In the antisolvent method, both methanol and water are polar solvents, with hydrogen bonding occurring between the molecules, where the hydrogen of one molecule is weakly covalently bonded to the oxygen of another. Nanococrystals prepared by this method exhibited greater solubility compared to the pure drug, since the addition of antisolvent reduces solute solubility in the system, thereby facilitating cocrystal formation (Bhandari et al., 2020)

In summary, solvent selection plays a decisive role in nanococrystal preparation, as it governs not only crystallization efficiency but also particle size, morphology, and residual solvent content. Both empirical and computational approaches, such as COSMO-RS, have proven useful in guiding solvent choice to improve process efficiency and performance. Careful consideration of solvent properties, including solubility, polarity, and boiling point, is therefore essential to ensure successful nanococrystal formation with optimal physicochemical and biopharmaceutical characteristics.

3. Nanococrystal Fabrication and Production

The method of nanococrystal preparation plays a crucial role in producing products of appropriate quality. The preparation process can be carried out in either two separate stages or a single stage. In general, the two-stage process is more commonly employed, beginning with the formation of cocrystals followed by particle size reduction to the nanometer range. However, some studies have also utilized a single-stage approach to enhance process efficiency.

3.1. Solvent evaporation

Solvent evaporation is great method for producing cocrystal formation. It can mediate the interaction between API and coformer in solvent resulting great cocrystal formation. The solvent evaporation method was applied in the preparation of itraconazole–succinic/fumaric acid and indomethacin–saccharin/nicotinamide nanococrystals. In both cases, solvent evaporation was combined with wet milling and resulted in significant improvements in solubility and dissolution rate. No variations in process parameters were reported, and the method was primarily used for the formation of nanococrystals with enhanced solubility (Z. Huang et al., 2022). Modification of solvent evaporation with some induced energy such as microwave show great promise in producing nanococrystal of diclofenac and prolime with diameter around 300 nm range with drug release increased modestly under different pH conditions (Nugrahani & Auli, 2020).

3.2. Anti-solvent

Antisolvent-based methods were widely employed and revealed several critical effects of process parameters. In the case of carbamazepine–nicotinamide nanococrystals, sonication was found to reduce particle size by inducing high-energy breakage, while temperature exerted a marked effect, with higher processing at 60 °C yielding smaller particles due to faster solvent evaporation. Interestingly, stirring speed did not produce a significant change (Thakor et al., 2020). Carvedilol–tartaric acid nanococrystals demonstrated strong dependence on the water/acetone ratio, in which higher ratios yielded smaller particles, although the effect was influenced by drug concentration. Stabilizer concentration was also crucial, since low levels of poloxamer generated smaller particles, whereas higher levels increased viscosity and resulted in larger particles. The freezing rate during lyophilization had an additional effect, with slow freezing in the presence of trehalose or PEG providing enhanced stability (Mohammady et al., 2021). Paclitaxel–disulfiram nanococrystals were prepared using antisolvent precipitation, forming stable particles of approximately 160 nm, though no process variables were explored (Mohammad et al., 2018). Ezetimibe–maleic acid nanococrystals use antisolvent as the second step to produce nanoparticle, the cocrystal formation was done using solvent evaporation (Bhandari et al., 2020). Overall, antisolvent methods were effective for producing highly soluble nanococrystals, and solvent ratios, stabilizer concentration, and freezing conditions were particularly important parameters.

3.3. Mechanical

Mechanical methods, including grinding and milling, were employed in multiple systems and revealed diverse process-dependent outcomes. For naproxen–

nicotinamide nanococrystals, the material of the grinding vessel, whether stainless steel or zirconium oxide, had little influence on particle size. Grinding time mainly affected morphology without major size changes (Santos et al., 2022). Lamivudine–zidovudine nanococrystals were highly sensitive to milling conditions. Milling time and the number of balls determined the extent of aggregation, with excessively long milling leading to Ostwald ripening, whereas an optimal balance ensured size reduction without destabilization (Witika et al., 2020). Other cases, such as carbamazepine–saccharin (Kojima et al., 2018), carbamazepine/indomethacin/furosemide (Karashima et al., 2016), and phenazopyridine–phthalimide (Y. Huang et al., 2017), demonstrated the successful use of wet milling or grinding to produce stable nanosuspensions or ultrafine particles, but without detailed parameter variation. For diclofenac–proline systems, mechanical routes including liquid-assisted grinding and neat grinding failed to produce the nanococrystal (Nugrahani & Auli, 2020). Collectively, mechanical approaches proved versatile, with milling time, or vessel material identified as critical process variables.

3.4. High Pressure Homogenization

High-pressure homogenization was applied in the formation of baicalein–nicotinamide and 4-aminosalicylic acid–sulfamethazine nanococrystals. In the former, the method produced amorphous nanosized particles with significantly improved dissolution and bioavailability (Pi et al., 2019; Salem et al., 2021). The former yielded nanosized, needle-like cocrystals with a narrow distribution. No specific process parameters were reported in either study, but the method was shown to be effective for producing nanosized cocrystals with superior dissolution performance compared to their microscale counterparts (Pi et al., 2019).

3.5. Other methods

Several methods are also known to be capable of modifying crystallization into the nanometer range. One such method employs a nano-crystallizer, in which crystallization occurs within a specific “template.” This template can lead to a reduction in surface free energy, thereby enabling the formation of relatively metastable new polymorphs. For example, urea–succinic acid cocrystals under normal conditions form in a 2:1 ratio; however, through this method, metastable cocrystals in a 1:1 ratio can be produced. The method is also capable of generating extremely small sizes, below 1 nm (Q. Yu et al., 2021).

4. Nanococrystal characterization

The quality of a product can be determined through a series of characterization processes. Appropriate characterization is essential to ensure accurate interpretation of results. Critical attributes in nanococrystals include solid-state properties, particle size, and morphology. In addition, supplementary tests may be conducted depending on the intended final dosage form of the nanococrystals.

4.1. Solid state characterization

One of the key parameters of nanococrystal products is solid-state characterization, which is essential to confirm the formation of a new crystalline phase as expected. Several methods can be employed to characterize this phenomenon, both thermal and non-thermal. A solid phase exhibits unique thermal

properties, and changes in these properties are indicative of the formation of a new crystalline phase. Such changes can be characterized using methods such as Differential Thermal Analysis (DTA), Thermogravimetric Analysis (TGA), or Differential Scanning Calorimetry (DSC) (Susanto et al., 2024).

Cocrystals are identified by the presence of two or more molecules within a single crystal lattice bound through non-covalent interactions. Therefore, crystal lattice testing represents the primary characterization method for cocrystals. X-Ray Diffraction (XRD) is one of the most powerful tools for evaluating the crystallinity of a material. Powder XRD provides insights into the crystalline aspects of a substance. However, it cannot produce crystal structure, single crystalline X-ray Diffraction should be utilized to give understanding of the crystal structure (Y. Wang et al., 2022).

The use of FTIR in cocrystal analysis allows the identification of new bond formation, which is demonstrated by the appearance of new peaks that differ from those of the original API but correspond to those of the cocrystal. Distinct fingerprint regions between the nanococrystal and the pure API indicate changes in molecular vibrations due to the establishment of new non-covalent bonds with the coformer (Witika et al., 2020).

Raman spectroscopy is another essential technique for pharmaceutical cocrystal characterization, particularly due to its ability to provide comprehensive insights into molecular interactions and solid-state identification. Through molecular vibration analysis, this technique enables the differentiation of cocrystal spectra from those of their individual components (drug and coformer), as evidenced by shifts in peak positions or changes in peak intensities. These phenomena reflect the formation of new non-covalent interactions, such as hydrogen bonding, which underlie cocrystal formation. Additional advantages of this method include its non-destructive nature, rapid analysis, and applicability in situ, allowing the monitoring of phase transformations and solid-state stability during formulation and storage (Karashima et al., 2016).

X-ray Photoelectron Spectroscopy (XPS) can also be employed to distinguish cocrystals from salts due to its sensitivity to changes in the chemical environment of individual atoms. The principle of XPS analysis is based on the absorption of photons of specific energy by electrons in the sample, which are then emitted from the solid. Analysis of the kinetic energy of these emitted surface electrons provides information regarding the chemical state of atoms at the surface. In cocrystal formation, the absence of proton transfer indicates that the newly formed phase can be categorized as a cocrystal (Witika et al., 2020).

Comprehensive solid-state characterization is essential to confirm the successful formation of nanococrystals and to distinguish them from other solid forms. Techniques such as DSC, XRD, FTIR, Raman spectroscopy, and XPS provide valuable information ranging from thermal behavior and crystal structure to molecular interactions and surface chemistry. The combined use of these analytical methods allows for a thorough understanding of the new crystalline phase, supporting the identification, stability, and quality of nanococrystal products.

4.2. Particle size

One of the key parameters of nanosized formulations is particle size itself. An optimal particle size is considered to be below 200 nm. However, by definition, nanoparticles are particles with a size below 800 nm. A good polydispersity index (PDI) value is less than 0.1, which indicates a monodisperse system. Nevertheless, achieving monodispersity in pharmaceutical formulations is highly challenging, and values up to 0.4 are generally still considered acceptable (Witika et al., 2020). Particle size can be measured using several methods, such as dynamic light scattering (DLS), Laser Diffraction, or atomic force microscopy (AFM).

DLS and LD are more frequently employed because it provides results that are more representative. Dynamic Light Scattering (DLS) measures fluctuations in scattered light intensity over time at a fixed angle to determine particle diffusion and size. When particles are dispersed in an aqueous medium, a hydration layer forms, which can cause size readings to appear larger, particularly for solid-state samples. The choice of dispersion medium is critical, as both components must remain well suspended during measurement (Peltonen, 2018).

While DLS is well-suited for analyzing nanoscale particles in suspension, laser diffraction offers a complementary approach, especially for broader particle size distributions. This technique is widely used to characterize powders, suspensions, emulsions, and aerosols. It operates by analyzing how a laser beam is diffracted by dispersed particles, with the diffraction angle inversely related to particle size. The resulting scattering pattern is then processed to generate a full-size distribution profile (Susanto et al., 2024).

4.3. Morphology

Morphology is one of the critical parameters of nanococrystals, as differences in crystal habit or shape can significantly influence the physicochemical properties of a drug. Microscopy is among the most commonly used tools to assess morphology. However, optical microscopy is not suitable in this context due to the nanoscale size of the product, which requires more advanced imaging techniques.

Scanning Electron Microscopy (SEM) operates by scanning a focused beam of electrons across the sample surface and detecting secondary or backscattered electrons to generate detailed images of surface morphology. Transmission Electron Microscopy (TEM), in contrast, transmits electrons through an ultrathin sample and forms highly magnified images of the internal structure based on the transmitted electrons. These instruments can achieve magnifications ranging from tens of thousands to several hundred thousand times, making them particularly useful in nanococrystal research (Egerton, 2016). This technique can also provide insights into particle size. However, it is important to note that particle size measurements using microscopy may carry a risk of limited representativeness due to small sampling areas.

4.4. Performance test

Once the formation of nanococrystals has been confirmed through appropriate characterization techniques, further performance evaluations are necessary. These assessments typically involve solubility studies, dissolution testing, bioavailability analysis, and stability testing under various environmental conditions

to determine the extent to which the nanococrystals fulfill their intended pharmaceutical objectives.

5. Nanococrystals in Pharmaceutical Applications

5.1. Solubility

One of the most consistent advantages of nanococrystals is their capacity to improve drug solubility through particle size reduction and disruption of the crystal lattice. Several studies have highlighted dramatic improvements. Itraconazole–succinic and fumaric acid nanococrystals exhibited kinetic solubility values up to 20 to 30-fold higher than the raw drug, demonstrating superior dissolution kinetics compared to both nanocrystals and macro-cocrystals (Z. Huang et al., 2022). Indomethacin–saccharin and indomethacin–nicotinamide nanococrystals displayed solubility increases of more than 10-fold, with the latter maintaining supersaturation for extended periods due to strong intermolecular interactions (Z. Huang et al., 2022). Piperine–succinic acid nanococrystals showed a 12.7-fold increase in solubility, compared to a more modest 3.9-fold increase observed in cocrystals alone (Fitriani et al., 2022). Similarly, carvedilol–tartaric acid nanococrystals demonstrated an exceptional solubility enhancement of nearly 2000-fold relative to the pure drug, making this one of the most remarkable cases reported (Mohammady et al., 2021). Other notable systems include baicalein–nicotinamide nanococrystals, with solubility and dissolution improvements of approximately 2.5-fold (Pi et al., 2019), and ezetimibe–maleic acid nanococrystals, which exhibited an 18.8-fold increase in dissolution efficiency, achieving 95% release within 45 minutes (Bhandari et al., 2020).

5.2. Bioavailability

Beyond solubility, nanococrystals have been shown to markedly improve oral bioavailability. Paclitaxel–disulfiram nanococrystals enhanced cellular uptake 14-fold and produced nearly nine-fold dose reductions while maintaining efficacy, translating into improved pharmacological performance (Mohammad et al., 2018). Pazopanib–fumarate nanocrystalline micelles increased oral bioavailability three-fold compared to the parent drug, maintaining plasma concentrations above therapeutic levels for up to 30 hours, while also providing enhanced stability through high zeta potential values (Shen et al., 2023). Phenazopyridine–phthalimide nanococrystals increased oral bioavailability 2.4-fold compared to the cocrystal and salt forms (Y. Huang et al., 2017). In the case of baicalein–nicotinamide nanococrystals, oral bioavailability was enhanced by nearly six-fold compared to the coarse powder, outperforming both nanocrystals and cocrystals individually (Pi et al., 2019). Similarly, 5-fluorouracil–proline nanococrystals demonstrated solubility and permeability increases of 4.6- and 3.9-fold, respectively, leading to a 2.7-fold increase in oral bioavailability compared to cocrystals alone (Y.-M. Yu et al., 2022).

5.3. Stability

Stability enhancement represents another important advantage of nanococrystallization, ensuring better storage, handling, and performance of formulations. For instance, naproxen–nicotinamide nanococrystals showed improved morphological stability when stabilized with surfactants such as Tween® 85 and Span® 85, with wet milling producing more stable dispersions than grinding

(Santos et al., 2022). Carvedilol–tartaric acid nanococrystals also exhibited superior stability when lyophilized with trehalose or PEG, which protected the crystalline form while minimizing crystal growth during freezing (Mohammady et al., 2021). Pazopanib–fumarate nanocrystalline micelles showed strong colloidal stability with a zeta potential of 62 mV, retaining integrity during accelerated stability studies (Shen et al., 2023). Similarly, lamivudine–zidovudine nanococrystals exhibited nanosuspensions with zeta potentials around −42 mV, correlating with excellent physical stability and reduced aggregation, while also lowering toxicity compared to single-drug mixtures (Witika et al., 2020). Carbamazepine, indomethacin, and furosemide nanococrystals retained their crystalline structures even under high-energy milling conditions, maintaining physical stability alongside enhanced dissolution (Karashima et al., 2016).

Table 1. Summary of Pharmaceutical Application of Nanococrystal

No	API	Method	Result	References
1	Paclitaxel-Disulfiram	Antisolvent precipitation	Optimum diameter 160 nm, stable, 14× higher uptake vs paclitaxel nanocrystal, 5× apoptosis activity, 9× IC50 reduction	(Mohammad et al., 2018)
2	Itraconazole-fumaric acid Itraconazole-succinic acid Indomethacin-saccharin Indomethacin-nicotinamide	Solvent evaporation - Wet milling	Itraconazole SUC nanococrystal solubility ↑30×; IND-SAC/NCT nano-CC solubility ↑10–12×, sustained supersaturation	(Z. Huang et al., 2022)
3	Urea- Succinic acid	Nano-crystallizer	Produced <100 nm particles, metastable polymorphs (1:1 ratio)	(Q. Yu et al., 2021)
4	Piperine- Succinic acid	Wet milling	344 nm particles, solubility ↑12.7× vs piperine, dissolution rate ↑2×	(Fitriani et al., 2022)
5	Naproxen-Nicotinamide	Assisted grinding - Wet milling	Improved morphology, surfactant-assisted systems gave smaller & stable dispersions	(Santos et al., 2022)
6	Carbamazepime-Nicotinamide	Anti solvent	Nanococrystals D50 ~138 nm, dissolution superior to cocrystal and PM	(Thakor et al., 2020)
7	Carvedilol-Tartaric acid	Anti-solvent	Ultra-fine NCCs ~1 nm, solubility ↑~2000×	(Mohammady et al., 2021)
8	Carbamazepime-Saccharin	Wet milling	Stable nanosuspension via steric/electrostatic stabilization	(Kojima et al., 2018)
9	Pazopanib-fumarate disodium glycyrrhizinate	Liquid assisted ball milling	Nanocrystalline micelles, solubility ↑, bioavailability ↑3×, stable (ZP -62 mV)	(Shen et al., 2023)
10	Cytarabine- Uracil	• Liquid assisted milling • Grinding + solvent evaporation • Antisolvent	Block-shaped nanococrystal (563 nm), permeability ↑, retention t½ ↑1.7×, solubility decrease compensated by nanosizing	(Y.-M. Yu et al., 2023)

No	API	Method	Result	References
11	Carbamazepime-saccharin Indomethacin-saccharin Furosemide-caffeine Furosemide-xytosine nano-salt suspension	Wet milling using nano pulverizer	Nanococrystal suspensions <200 nm, improved dissolution, crystalline structure maintained	(Karashima et al., 2016)
12	5-fluorouracil-Proline	Solvent-assisted grinding and solution evaporation	Nano-micelles (146 nm), solubility ↑4.6×, bioavailability ↑2.7×	(Y.-M. Yu et al., 2022)
13	Baicalein-Nicotinamide	Slurry cocrystal continued by High Pressure Homogenization	Nanococrystal ~252 nm, dissolution ↑2.5×, bioavailability ↑6×	(Pi et al., 2019)
14	Sulfamethazine - 4-aminosalysiclic	High Pressure Homogenization and high power ultrasound	Needle-like crystals, High Pressure Homogenization produced nanoscale, improved dissolution	(Salem et al., 2021)
15	Phenazopyridine-pthalimide	Slow evaporation and centrifugation	21 nm nanococrystal, improved release, bioavailability ↑2.4×	(Y. Huang et al., 2017)
16	Diclofenac-Proline	Liquid assited grinding	Physical mixture	(Nugrahani & Auli, 2020)
		Neat grinding	Cocrystal diameter 867.9 nm PI 0.353 nm	
		Globule inversion phase	Physical mixture 310 nm PI 0.316	
		Fast evaporation assisted microwaving	598 nm particles, drug release ↑1.3–2.5× (pH dependent)	
17	Ezetimibe-oxalic acid Ezetimibe-succinic acid Ezetimibe-maleic acid	Solvent evaporation and antisolvent	Nanococrystal ~226 nm, dissolution efficiency ↑18.8×, 95% release in 45 min	(Bhandari et al., 2020)
18	Lamivudine-Zidofudine	Solvent evaporation and wet milling	Nanococrystal ~271 nm, stable nanosuspension (Zeta Potential −42 mV), dissolution improved, toxicity reduced	(Witika et al., 2020)

Conclusion

Nanococrystals represent a promising advancement in pharmaceutical formulation by integrating the complementary benefits of cocrystals and nanocrystals. Through careful selection of active pharmaceutical ingredients, coformers, stabilizers, and solvents, nanococrystals can be designed to achieve improved physicochemical stability and optimized performance. A wide range of fabrication techniques, including antisolvent precipitation, wet milling, high pressure homogenization, and spray flash evaporation, have demonstrated success in

producing nanoscale systems with desirable properties. Characterization using thermal, spectroscopic, and microscopic techniques is essential to confirm crystalline structure and ensure product quality. Evidence from recent studies consistently shows that nanococrystals provide remarkable improvements in solubility, dissolution, and oral bioavailability compared to conventional forms. These findings highlight nanococrystals as a versatile and effective strategy for enhancing drug delivery. Continued research focusing on formulation design and optimization will further support the development of clinically viable nanococrystal-based pharmaceutical products.

Declaration of Competing Interest

The authors declare that they have no competing interests

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