

FORMULATION CHALLENGES IN ANTI-DIABETIC DRUG – A SOLUTION THROUGH NANO-COCRYSTAL APPROACH

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ABSTRACT

Nano-cocrystals combine the advantages of co-crystallization and nanotechnology to enhance the solubility, dissolution, bioavailability and stability of poorly soluble drugs. These nanoscale crystalline structures, consisting of an API and a coformer, improve drug absorption without altering pharmacological properties. Preparation methods include top-down approaches like high-pressure homogenization and milling, as well as bottom-up techniques such as anti-solvent precipitation and spray drying. Characterization using DSC, IR spectroscopy and microscopy ensures precise evaluation. Nano-cocrystals offer promising applications in oral and intravenous drug delivery, addressing challenges like poor solubility and frequent dosing. In anti-diabetic drug formulations, they enhance dissolution and controlled release, improving therapeutic efficacy and patient compliance. Additionally, targeted nano-cocrystals in cancer therapy improve drug stability and overcome chemotherapy resistance. Despite challenges in production, scalability and regulatory approval, nano-cocrystals represent a transformative approach in modern drug delivery.

KEYWORDS: Nano-cocrystals, solubility enhancement, bioavailability, drug delivery, anti-diabetic drugs, cancer therapy, high-pressure homogenization, spray drying, controlled release.

INTRODUCTION

In the pharmaceutical industry, active pharmaceutical ingredients (APIs) are predominantly administered in solid form. To address challenges such as poor solubility, low dissolution rates, inadequate mechanical properties, hygroscopicity, and limited physical and chemical stability, researchers and pharmaceutical companies are continually developing new drug formulations. Approximately 60% of commercial drugs currently face issues related to poor aqueous solubility, prompting efforts to enhance both pharmaceutical and biological properties. Co-crystals have emerged as a promising approach for improving solubility, with studies showing solubility enhancements ranging from 4 to 20 times. Moreover, co-crystal formation can improve the physical properties of drugs while preserving their original pharmacological effects.^[1]

Nanocrystals, which are nano-sized drug particles stabilized by surface stabilizers, have been extensively studied for their ability to enhance saturation solubility, dissolution rates, oral bioavailability, and biological activity. These nanocrystals are typically produced using either top-down or bottom-up approaches. Top-down methods include wet media milling and high-pressure homogenization, while bottom-up techniques primarily involve anti-solvent precipitation. Both approaches are widely utilized to achieve nanosized crystals. The improvement in dissolution rate, resulting from the

reduction in particle size, is attributed to the increased surface area and reduced diffusion layer thickness.^[2]

Poorly soluble drugs often exhibit slow and inconsistent dissolution, which limits their absorption in the gastrointestinal tract. To address this challenge, extensive research is focused on improving drug solubility. Nanocrystals (NCs) offer significant advantages over conventional micron-sized drug powders, particularly for poorly soluble drugs. These benefits include enhanced bioavailability, improved absorption, reduced variability between fed and fasted states, faster onset of action, and minimized inter-subject variability, ultimately contributing to improved safety and efficacy.^[3]

Nanotechnology has been widely advanced to improve the solubility of active pharmaceutical ingredients, while co-crystal engineering has emerged as a pivotal approach in modern drug design. The integration of these two techniques into "nano co-crystallization" presents a promising strategy, combining their strengths to deliver enhanced drug properties and performance.^[4]

NEED FOR NANO-COCRYSTAL

- Co-crystals improve the properties of active pharmaceutical ingredients (APIs) such as solubility, melting point, bioavailability, stability, and dissolution rate without modifying covalent bonds.
- While salt formation relies on the presence of acidic,

basic, or ionizable sites to enhance solubility, cocrystals can be formed without the need for these functional groups.^{[5][6]}

STRUCTURE OF NANO-COCRYSTAL

Nano-cocrystals are nanoscale crystalline structures consisting of an active pharmaceutical ingredient (API) and a coformer, designed to improve the solubility and bioavailability of poorly soluble drugs. These structures feature a precise stoichiometric arrangement of API and coformer molecules, stabilized by non-covalent interactions, including hydrogen bonding, π - π stacking, and van der Waals forces.^[7]

The nanoscale dimensions of these cocrystals greatly enhance the surface area-to-volume ratio, resulting in faster dissolution rates and improved bioavailability. This is especially advantageous for drugs with low water solubility, as the smaller particle size enables quicker dissolution in biological fluids.^[1]

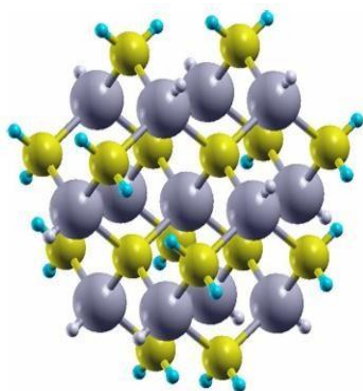


Figure 1: Structure of a typical nanocrystal.

The structure of a typical nanocrystal, as considered in our study, consists of cations and anions represented as large spheres in various colours as shown in figure 1. The surface layer is capped with hydrogen atoms, depicted as small spheres.^[8]

- **Cocrystal Lattice:** The molecular arrangement within a nanococrystal adheres to a defined crystal lattice, akin to that of traditional cocrystals. This lattice is governed by the intermolecular interactions between the various components of the nanococrystal.
- **Nanoscale Dimensions:** Nanococrystals possess sizes within the nanometer range, offering a substantially larger surface area compared to traditional micron-sized crystals. This increased surface area enhances properties such as dissolution rate and bioavailability.^[1]
- **Stoichiometric Ratio:** The components of the nanococrystal are combined in a fixed stoichiometric proportion, which is critical for ensuring the material's stability and desired properties.^[1] Selecting an appropriate co-former for cocrystal development can be a complex task. The "tactless" cocrystal screening approach utilizes a library of

approved chemicals for co-former selection. Once a suitable cocrystal with improved properties and compatibility is identified, it can be developed into a dosage form. Co-former selection often relies on a trial-and-error method.

ADVANTAGES OF NANO-COCRYSTALS

1. **Improved Solubility and Dissolution Rates:** The combination of nanocrystal and cocrystal approaches synergistically enhances kinetic solubility and dissolution rates, leading to better drug absorption.^[9]
2. **Enhanced Bioavailability:** By increasing the dissolution rate, nano-cocrystals improve the bioavailability of active pharmaceutical ingredients (APIs), ensuring more efficient delivery of the drug to the target site.^[9]
3. **Carrier-Free Delivery:** Nano-cocrystallization offers a flexible technique for delivering poorly soluble medicines without the need for additional carriers, simplifying the formulation and potentially reducing side effects.^[10]
4. **Controlled Polymorphism and Enhanced Stability:** Techniques like liquid-assisted milling in nano-cocrystal production can improve product performance by controlling polymorph formation and increasing crystallinity, leading to enhanced stability.^[1]
5. **Versatile Production Methods:** Continuous processes such as Spray Flash Evaporation enable the efficient preparation of pharmaceutical nano-cocrystals, facilitating scalability and consistent quality in production.^[7]

DISADVANTAGES OF NANO-COCRYSTALS:

1. **Complex Production Processes:** The preparation of nano-cocrystals often involves sophisticated techniques such as high-pressure homogenization, precipitation, and milling methods. These processes can be technically demanding and may require specialized equipment.^[11]
2. **Stability Issues:** Nano-cocrystals can face stability challenges, including particle aggregation and potential amorphization during processing. These issues can affect the consistency and efficacy of the final pharmaceutical product.^[12]
3. **Scalability Concerns:** Translating laboratory-scale nano-cocrystal production to industrial-scale manufacturing can be challenging. Ensuring uniformity and maintaining the desired physicochemical properties during large-scale production require careful optimization.
4. **Regulatory Hurdles:** The introduction of nano-cocrystal formulations may encounter regulatory challenges, as comprehensive guidelines specific to these systems are still evolving. Demonstrating safety, efficacy, and quality to meet regulatory standards can be a complex process.

FORMATION OF NANO-COCRYSTALS

- 1. Selection of Co-former:** Choosing an appropriate co-former is crucial. The co-former should possess functional groups capable of forming non-covalent interactions, such as hydrogen bonds, with the API. This selection is guided by the desired enhancement in solubility, stability, and bioavailability.^[13]
- 2. Preparation Methods:** Common techniques for nano-cocrystal formation include:
 - **Solvent Evaporation:** Dissolving both the API and co-former in a suitable solvent and then evaporating the solvent under controlled conditions.
 - **Co-grinding:** Mechanically grinding the API and co-former together to induce cocrystallization.
 - **Supercritical Fluid Technology:** Utilizing supercritical fluids to facilitate the formation of nano-cocrystals.^[14]
- 3. Characterization:** After formation, nano-cocrystals are characterized using techniques such as X-ray diffraction (XRD), scanning electron microscopy (SEM), and differential scanning calorimetry (DSC) to confirm their structure and properties.

APPLICATION OF PHARMACEUTICAL NANO-COCRYSTAL

Pharmaceutical nano-cocrystals have emerged as a transformative approach to enhance the delivery of poorly soluble drugs, addressing a longstanding challenge in the pharmaceutical industry. By engineering active pharmaceutical ingredients (APIs) into nano-sized cocrystals with suitable co-formers, significant improvements in solubility, dissolution rates, and bioavailability can be achieved. This advancement not only enhances therapeutic efficacy but also holds substantial market potential for the development of novel drug formulations.^{[15][16][17]}

1. Drug delivery

Oral administration is widely regarded as the safest and most convenient method of drug delivery.^[18] Nanocrystals, with their large surface area, can significantly enhance the saturation solubility of drugs, leading to improved dissolution rates. Studies report that nanocrystal tablets can achieve up to a 21% increase in oral bioavailability.^[19] Research indicates that itraconazole- adipic acid nano-cocrystals exhibit higher oral bioavailability compared to amorphous formulations.^[20] while phenazopyridine-phthalimide nanocrystals demonstrate 2.44 times greater bioavailability than coarse suspensions.^[20] In Müller's work, nanocrystals were incorporated into a solid polyethylene glycol (PEG) matrix, ground into fine powder, and subsequently compressed into tablets or encapsulated.^[21] This innovative drug delivery system facilitates the direct integration of poorly soluble drugs into tablets, capsules, or hot-melt solid matrices, significantly enhancing their oral bioavailability. Intravenous (IV) drug delivery is recognized as one of the most effective administration routes due to its low dosage requirements and exceptional bioavailability.

Unlike oral or other delivery methods, IV administration bypasses absorption barriers, allowing the drug to directly enter systemic circulation, ensuring rapid and complete drug action. However, the development of IV formulations often faces challenges associated with the use of toxic solvents or excipients necessary to dissolve poorly soluble drugs. These harmful additives can limit the safety and applicability of IV therapies, posing risks such as toxicity or adverse reactions.

Nanocrystals offer a promising solution to this problem. Since nanocrystals are composed of the pure drug stabilized by minimal excipients like surfactants or polymers, they eliminate the need for harmful solvents.^{[22][23]}

This makes them an ideal candidate for IV administration, offering a safer and more efficient alternative. Additionally, the nanoscale size ensures a high surface area, enabling rapid dissolution and improved pharmacokinetic profiles. The use of nanocrystals for IV delivery not only improves drug solubility and bioavailability but also minimizes potential side effects associated with conventional formulations, broadening their applicability for a wide range of poorly soluble drugs.

2. Targeted nano-cocrystals

Cancer continues to affect a growing number of patients globally, with projections indicating that the number of cases could rise to 13.2 million by 2030. Chemotherapy remains one of the primary treatment methods for cancer. However, its efficacy is often hindered by drug resistance, which limits its broader application. To address this challenge, researchers have developed various cytotoxic drugs specifically targeting cancer cells. Unfortunately, many of these drugs suffer from poor solubility and low bioavailability in vivo, reducing their therapeutic potential. Nano-crystals have emerged as a promising solution to these issues, offering superior solubility and bioavailability, making them effective candidates for targeted cancer therapies. Meghna, using high-pressure homogenization, successfully prepared a nanosuspension of PIK75. This formulation demonstrated an 11-fold increase in saturated solubility and improved stability in plasma, highlighting the potential of nano-crystals in enhancing the efficacy of chemotherapy drugs.^[24]

PREPARATION METHODS OF PHARMACEUTICAL NANO-COCRYSTALS

Pharmaceutical nano-cocrystals are typically prepared using two main approaches: top-down and bottom-up techniques. The top-down methods involve breaking down larger particles into nanosized structures. Common techniques in this category include ball milling, which utilizes shear forces to reduce particle size, and high-pressure homogenization, where intense mechanical forces are applied to achieve nanoscale dimensions. On the other hand, the bottom-up approach focuses on

building nano-cocrystals from molecular or atomic precursors as shown in Figure 2. A widely used bottom-up technique is precipitation, which relies on the processes of nucleation and crystal growth to form nano-sized crystals.

In the top-down approach, ball milling is often carried out using specialized equipment where the drug and stabilizers are milled in the presence of grinding media, ensuring consistent particle size reduction. High-pressure homogenization, alternatively, forces the drug suspension through narrow gaps under extreme pressure, creating high shear and cavitation forces to break the particles. These methods are particularly advantageous

for drugs with high crystallinity and low solubility, as they enhance bioavailability by increasing surface area.

The bottom-up approach, exemplified by precipitation, involves the dissolution of drug and coformer materials in a suitable solvent followed by rapid mixing with an antisolvent. This triggers supersaturation, leading to nucleation and subsequent growth of nano-cocrystals. Careful control over process parameters such as solvent selection, temperature, and mixing speed is critical to achieve uniform crystal size and stability. This approach is highly versatile and is often used to produce nano-cocrystals with precise control over size and morphology.

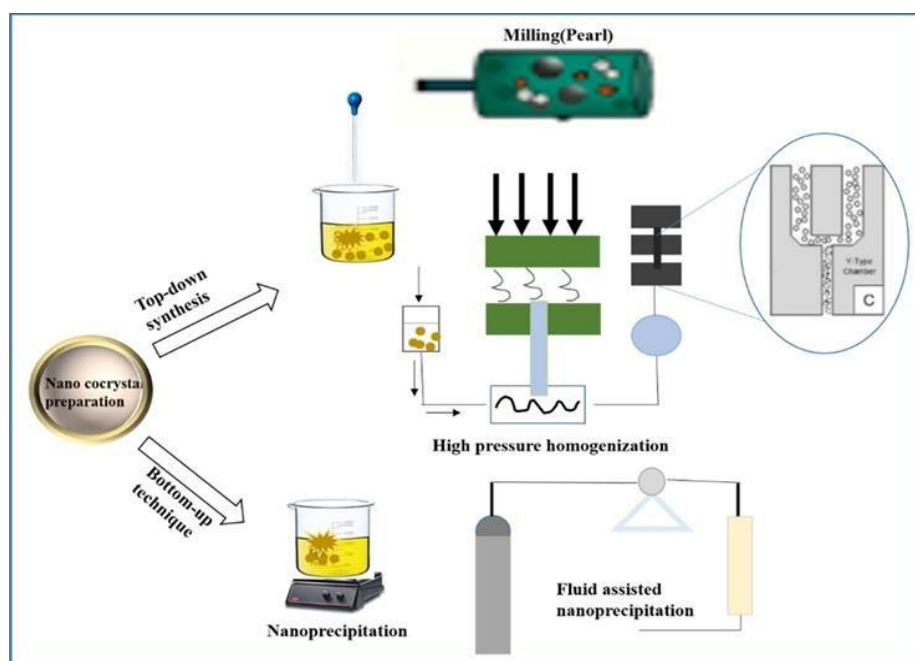


Figure 2: Schematic representation of the formation of pharmaceutical nano-cocrystals.

I. TOP-BOTTOM SYNTHESIS

1. High-Pressure Homogenization Technique

High-pressure homogenization (HPH) is a versatile and widely utilized technique for the production of nanosized crystals, particularly in the pharmaceutical industry, to address the challenges of poor solubility and bioavailability associated with many drug molecules. By applying intense shear forces and cavitation during the homogenization process, this method effectively reduces particle size, leading to an increased surface area and improved dissolution rates. In recent studies, HPH has demonstrated its potential for preparing nano-cocrystals to enhance drug delivery. For instance, using poloxamer 188 as a stabilizer, nano-cocrystals of baicalein (BE) and baicalein-nicotinamide (BE-NCT) have been successfully formulated. Poloxamer 188 acts as a surfactant, preventing particle aggregation and ensuring the stability of the nanosuspension. These nano-cocrystals exhibit significantly enhanced solubility and dissolution profiles, which translate into improved oral bioavailability. The ability of HPH to produce high-quality, uniform nano-cocrystals highlights its

importance as a promising approach in modern drug formulation strategies.^[2] Praziquantel has been successfully formulated using the high-pressure homogenization (HPH) technique with various stabilizers. Following an extensive screening process, two promising formulations were identified, combining poloxamer 188 with either polyvinylpyrrolidone (PVP) or maltodextrin. These combinations demonstrated effective stabilization and enhanced the formulation's overall performance.^[25]

While the HPH method is effective for producing nanosized crystals, it is not yet fully optimized for widespread application. Key limitations of this technique include its high energy demands, time-intensive processes, and challenges in achieving consistently uniform nanoparticle sizes.

2. Milling

Solid-State Milling: Solid-state milling involves mixing cocrystal solid materials in an appropriate stoichiometric ratio and then grinding them using tools such as a mortar

and pestle, ball mill, or vibration mill. This process does not require the use of solvents and typically takes around 30–60 minutes. The solid-state milling method is highly effective in producing a variety of cocrystals. It reduces particle size while significantly increasing the specific surface area. Compared to dissolution-based cocrystal preparation methods, solid-state milling offers superior selectivity. Furthermore, it is straightforward to perform, enabling the rapid and efficient production of cocrystal products. In Andrew's study, small quantities of solvent were incorporated to enhance the kinetics of solid-state cocrystallization and to achieve polymorph control, a factor of great importance in the pharmaceutical field. Using this modified solid-state grinding approach, he successfully produced organic cocrystals.^[26] Braga reported that the cocrystals prepared have the potential to enhance solubility and thermal stability, contributing valuable advancements in the field of traditional solid-state chemistry. Similarly, Jug demonstrated that solvent-free grinding is an efficient method for creating solvent-free cyclodextrin inclusion complexes.^{[27][28]} Solid-state grinding is a viable alternative for the successful

preparation of nano-cocrystals; however, it has certain limitations, including the tendency for particles to form and aggregate within the micrometer range.^[29]

Liquid-assisted milling is a technique used to improve the polymorphism of the crystal system by incorporating a small amount of solvent during the grinding process.^[30] The solvent in liquid-assisted milling plays a key role in accelerating catalytic actions. Its main advantage is enhancing the product's performance, controlling polymorph formation, and increasing the crystallinity of the product. This method is particularly effective for the formation and preparation of cocrystals. Additionally, it can improve the crystallization rate, making it especially suitable for materials that exhibit poor crystallization behavior when processed by pure grinding.^[31] This method is an excellent option for preparing cocrystals with high purity and offers selectivity in the formation of polymorphic cocrystals. By introducing solvents of varying polarity, the crystalline polymorph can be transformed into a different organic component.

II. BOTTOM-UP SYNTHESIS

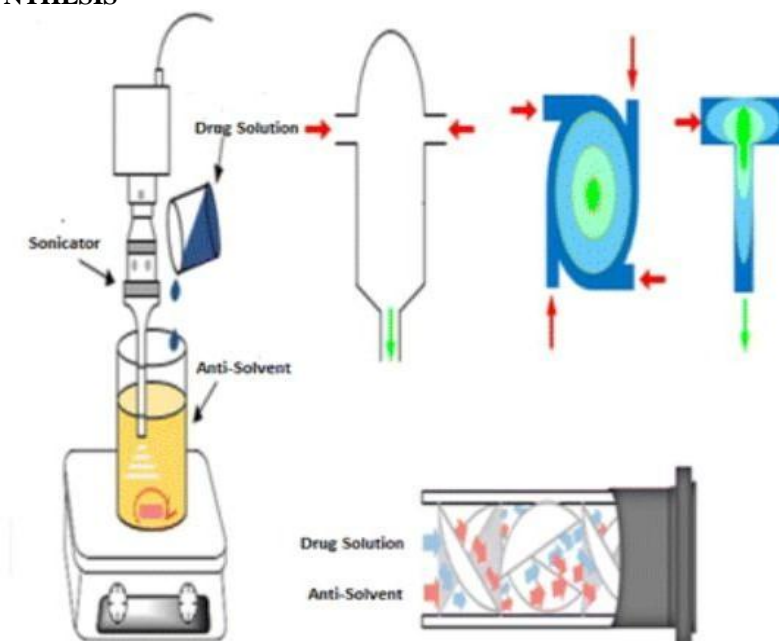


Figure 3: Schematic representation of formulation of nano-cocrystals by Anti-solvent technique.

Anti-Solvent Precipitation Technique

Anti-solvent Precipitation: The precipitation method is frequently employed for preparing nano-cocrystals, particularly in systems where soluble and insoluble components are combined during cocrystal formation shown in Figure 3. Given the varying solubilities of the cocrystal components in aqueous solutions, achieving the stable preparation of nano-cocrystals presents a significant challenge.^[32] To achieve stable nano-cocrystals with the desired particle size, an anti-solvent system combined with a stabilizer is carefully selected and introduced. Due to the varying solubilities of the cocrystals in the solvent and anti-solvent, the addition of

the anti- solvent to the system significantly increases the likelihood of cocrystal precipitation.^[33] The absence of systematic studies on the selection of anti-solvents has hindered the widespread application of this method in the medical field. Therefore, choosing the appropriate anti-solvent is a crucial step in the preparation of nano-cocrystals.

III. SPRAY DRYING METHOD (SD):

Spray drying is a continuous and scalable process commonly used for producing dry powders. It begins with atomizing a liquid feed into tiny droplets using an atomizer. These droplets are then exposed to hot gas,

which rapidly evaporates the solvent, leaving behind dry particles. This method is both economical and efficient, making it suitable for large-scale production. It is widely used in various industries, including pharmaceuticals and food processing.^{[34][35]} Spray drying (SD) has found extensive applications in the food, cosmetics, and pharmaceutical industries. It is also employed in the preparation of pharmaceutical cocrystals, where it helps in producing uniform and stable formulations. This versatility makes SD a valuable technique for enhancing product properties and scalability in various sectors.^{[35][36][37]} Conventional spray dryers are limited in their ability to produce drug particles smaller than 2 micrometers. However, the Nano Spray Dryer B-90 is capable of successfully producing drug nanoparticles.^{[38][39]} This advancement makes the spray drying (SD) technique an attractive and effective method for fabricating pharmaceutical cocrystals, offering enhanced control over particle size and formulation.

ADVANCED CHARACTERIZATION TECHNIQUE

1. Thermal Analysis:

The primary applications of Differential Scanning Calorimetry (DSC) include analyzing phase transitions, determining melting points, glass transitions, and Curie points, assessing crystallinity, conducting kinetic studies, monitoring drug transformations, evaluating physical stability, and ensuring purity control.^[40] DSC is the most commonly used method in thermal analysis, valued for its speed, simplicity, and user-friendly operation. Its versatility makes it an essential tool for studying thermal properties across various applications.^[41] The DSC test is essential for analyzing polymorphisms and their stability, while TGA measures weight changes to detect solvent or hydrate structures. Rohani studied theophylline-nicotinamide cocrystals, noting distinct melting points (theophylline: 271.4°C, nicotinamide: 128.2°C). Nicotinamide melted first, leading to nucleation and growth of new crystals, which fully melted at higher temperatures.^[42]

2. Molecular Vibration Spectroscopy:

Molecular vibration spectroscopy, a subset of molecular spectroscopy, includes both infrared (IR) and Raman spectroscopy. The bond length and bond angle vary for different crystals, leading to differences in their vibration and rotational energies. As a result, vibration spectroscopy can be used to differentiate between crystals. The IR spectrum of various crystals shows variations in band absorption frequency, peak shape, peak position, and peak intensity.^[43] Common methods for preparing samples for IR spectroscopy include KBr pellets, the shake-flask method, the film method, and the liquid membrane method. Among these, the KBr pellet method is the most widely used for analyzing drug and food crystals. IR spectroscopy offers a simple and rapid approach to distinguishing crystal forms. In Guo's study, rod-shaped nanocrystals and spherical-like nanocrystals were prepared using sonoprecipitation and bead milling. IR spectroscopy, combined with other characterization

techniques, was then employed to examine the chemical structure of lovastatin, revealing no structural changes during the preparation process.^[44]

3. Microscopy Techniques:

Direct microscopic observation is a crucial analytical method for studying crystals in drugs and food. To date, five microscopy techniques have been applied in this field: polarizing microscopy (PLM), hot stage microscopy (HSM), atomic force microscopy (AFM), transmission electron microscopy (TEM), and scanning tunneling microscopy (STM). Compared to PXRD characterization, AFM and TEM are more sensitive techniques and are particularly effective for analyzing materials at the nanometer scale. Ricarte et al. used TEM to analyze the crystalline structure of griseofulvin in a solid dispersion with hydroxypropyl methyl cellulose acetate succinate. TEM provided real-space images and electron diffraction patterns, identifying griseofulvin crystals in the spray-dried dispersion. This study demonstrated that TEM is a valuable technique for characterizing crystalline structures, even at minimal levels of crystallization.^[45]

4. Solid-state NMR Spectroscopy

Solid-state NMR spectroscopy is a valuable tool for analyzing the dynamic behavior and chemical environment of atoms in crystals, making it essential for studying and determining crystal forms. In Pinon's study, solid-state NMR spectroscopy enhanced by dynamic nuclear polarization was used to investigate polymorphs and solvates of organic solids. The technique analyzed the effects of three polymorphs and one hydrated form on theophylline, a drug used to treat asthma.^[46]

FORMULATION CHALLENGES OF ANTI-DIABETIC DRUGS

1. **Poor Water Solubility:** Many anti-diabetic drugs, such as gliclazide, exhibit low aqueous solubility, leading to reduced bioavailability. Enhancing solubility is crucial for improving therapeutic efficacy. Techniques like solid dispersions with carriers like Aerosil 380 have been explored to address this issue.^[47]
2. **Short Half-Life and Frequent Dosing:** Some anti-diabetic medications have short biological half-lives, necessitating frequent dosing and potentially leading to patient non-compliance. Developing controlled-release formulations can help maintain consistent drug levels, reducing dosing frequency and improving adherence.
3. **Peptide Drug Delivery:** Delivering peptide-based drugs like insulin orally is challenging due to degradation in the gastrointestinal tract and poor absorption. Nanoparticulate-based drug delivery systems are being investigated to protect these peptides and enhance their bioavailability.^[48]
4. **Stability Issues:** Ensuring the chemical and physical stability of anti-diabetic drugs during formulation and storage is essential to maintain efficacy. Factors

such as temperature, humidity, and light exposure can affect drug stability, necessitating thorough stability testing and appropriate formulation strategies.

5. **Patient Compliance:** Complex dosing regimens and side effects can hinder patient adherence to anti-diabetic therapies. Formulating drugs with improved delivery methods, such as transdermal patches or long-acting injectables, can enhance convenience and compliance.
6. **Regulatory and Safety Concerns:** Innovative delivery systems, especially those involving nanotechnology, must undergo rigorous evaluation to ensure safety and efficacy. Addressing regulatory hurdles and long-term safety concerns is vital for the successful implementation of new formulations.^[49]

The nano-cocrystal approach offers promising solutions to several formulation challenges associated with anti-diabetic drugs:

1. **Enhancing Solubility and Dissolution Rates:** Many anti-diabetic drugs suffer from poor water solubility, leading to limited bioavailability. Nano-cocrystals, which are crystalline structures composed of the active pharmaceutical ingredient (API) and a coformer at the nanometer scale, significantly increase the drug's surface area. This enhancement facilitates a higher dissolution rate, thereby improving solubility and bioavailability.^[1]
2. **Improving Stability:** The cocrystallization process can enhance the physical and chemical stability of the drug. By selecting appropriate coformers, nano-cocrystals can protect the API from environmental factors such as humidity and temperature variations, which might otherwise degrade the drug.^[1]
3. **Facilitating Controlled Release:** Nano-cocrystals can be engineered to modulate the release profile of the drug. By manipulating the crystal structure and particle size, it's possible to design formulations that provide a sustained release of the medication, reducing the frequency of dosing and potentially improving patient compliance.^[1]
4. **Overcoming Biological Barriers:** The reduced particle size of nano-cocrystals allows for better permeation through biological membranes, enhancing oral absorption. This is particularly beneficial for drugs that face challenges in crossing gastrointestinal barriers.^[1]

The nano-cocrystal approach offers a promising solution to the formulation challenges of anti-diabetic drugs. By engineering drug particles at the nanometer scale, this method enhances solubility and dissolution rates, leading to improved bioavailability. Additionally, nano-cocrystals can provide controlled drug release, reducing dosing frequency and potentially improving patient compliance. This strategy addresses key issues in anti-diabetic drug formulation, offering a pathway to more effective therapies.

CONCLUSION

Pharmaceutical nano-cocrystals are a promising approach to enhancing drug solubility, stability, and bioavailability, making them a key focus for future drug discovery research. Despite their potential, there is a lack of systematic studies on their preparation and characterization. This review highlights common preparation methods and characterization techniques for nano-cocrystals. While high-pressure homogenization is a well-established method, it requires high energy consumption due to its high-pressure conditions. Emerging methods such as electrohydrodynamic atomization, spray drying, and the anti-solvent method offer great potential for efficient nano-cocrystal production. These newer approaches eliminate the need for stabilizers or desiccants, making them more sustainable and attractive options for advancing nano-cocrystal technology.

The nano-cocrystal approach effectively addresses key formulation challenges of anti-diabetic drugs. It enhances solubility, stability, and bioavailability, while enabling controlled drug release and improving patient compliance. By reducing particle size, nano-cocrystals also enhance absorption, offering a promising solution for more efficient and patient-friendly therapies.

REFERENCES

1. Tan J, Liu J, Ran L. A review of pharmaceutical nano co-crystals: A novel strategy to improve the chemical and physical properties for poorly soluble drugs. *Crystals*, 2021; 11(5): 1-14.
2. Pi J, Wang S, Li W, Kebebe D, Zhang Y, Zhang B, Qi D, Guo P, Li N, Liu Z. A nano- cocrystal strategy to improve the dissolution rate and oral bioavailability of baicalein. *Asian J. Pharm. Sci.*, 2019; 14(2): 154-64.
3. Jahangir MA, Imam SS, Muheem A, Chettupalli A, Al-Abbasi FA, Nadeem MS, Kazmi I, Afzal M, Alshehri S. Nanocrystals: Characterization overview, applications in drug delivery, and their toxicity concerns. *J. Pharm. Innov.*, 2020; 17(9): 1-2.
4. Nugrahani I, Auli WN. Diclofenac-proline nano-co-crystal development, characterization, in vitro dissolution and diffusion study. *Heliyon.*, 2020 1; 6(9): 48-64.
5. Patil S, Mhatre K, Shirode A, Kadam V. Pharmaceutical Co-Crystals: An Emerging Approach for Enhancement of Solubility and Bioavailability of a Drug. *Am. j. PharmTech Res.*, 2019; 9(5): 1-21.
6. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst Growth Des.*, 2009; 9(6): 2950-67.
7. Spitzer D, Risse B, Schnell F, Pichot V, Klaumünzer M, Schaefer MR. Continuous engineering of nano-cocrystals for medical and energetic applications. *Scientific Reports*, 2014 10; 4(1): 1-6.
8. Cherian R, Gerard C, Mahadevan P, Cuong NT,

- Maezono R. Size dependence of the bulk modulus of semiconductor nanocrystals from first-principles calculations. *Physical Review B— Condens. Matter Phys.*, 2010; 82(23): 1-7.
9. Huang Z, Staufienbiel S, Bodmeier R. Combination of co-crystal and nanocrystal techniques to improve the solubility and dissolution rate of poorly soluble drugs. *Pharm. Res.*, 2022; 39(5): 949-61.
 10. More A, Bade P, Darekar S. A review of pharmaceutical nano-cocrystal: a novel strategy to improve the chemical and physical properties for poorly water-soluble drugs. *J. Adv. Sci. Res.*, 2023; 14(02): 40-3.
 11. Bansal S, Bansal M, Kumria R. Nanocrystals: current strategies and trends. *Int J Res Pharm Biomed Sci.*, 2012; 3(1): 406-419.
 12. Gao L, Liu G, Ma J, Wang X, Zhou L, Li X, Wang F. Application of drug nanocrystal technologies on oral drug delivery of poorly soluble drugs. *Pharm. Res.*, 2013; 30(6): 1- 18.
 13. Singh M, Barua H, Jyothi VG, Dhondale MR, Nambiar AG, Agrawal AK, Kumar P, Shastri NR, Kumar D. Cocrystals by design: a rational coformer selection approach for tackling the API problems. *Pharmaceutics*, 2023; 15(4): 1-43.
 14. Schlosky KM. Supercritical phase transitions at very high pressure. *J. Chem. Educ.*, 1989 Dec; 66(12): 989.
 15. Ali HS, York P, Ali AM, Blagden N. Hydrocortisone nanosuspensions for ophthalmic delivery: a comparative study between microfluidic nanoprecipitation and wet milling. *JCR.*, 2011; 149(2): 175-81.
 16. George M, Ghosh I. Identifying the correlation between drug/stabilizer properties and critical quality attributes (CQAs) of nanosuspension formulation prepared by wet media milling technology. *Eur J Pharm Sci.*, 2013; 48(1-2): 142-52.
 17. Li Y, Wang Y, Yue PF, Hu PY, Wu ZF, Yang M, Yuan HL. A novel high-pressure precipitation tandem homogenization technology for drug nanocrystals production—a case study with ursodeoxycholic acid. *Pharm Dev Technol.*, 2014; 19(6): 662-70.
 18. Kesisoglou F, Panmai S, Wu Y. Nanosizing—oral formulation development and biopharmaceutical evaluation. *Adv. Drug Deliv. Rev.*, 2007; 59(7): 631-44.
 19. De Smet L, Saerens L, De Beer T, Carleer R, Adriaenssens P, Van Bocxlaer J, Vervaeke C, Remon JP. Formulation of itraconazole nanococrystals and evaluation of their bioavailability in dogs. *Eur J Pharm Biopharm*, 2014; 87(1): 107-13.
 20. Huang Y, Li JM, Lai ZH, Wu J, Lu TB, Chen JM. Phenazopyridine-phthalimide nano- cocrystal: Release rate and oral bioavailability enhancement. *Eur J Pharm Sci.*, 2017; 109: 581-6.
 21. Müller RH, Junghanns JU. Drug nanocrystals/nanosuspensions for the delivery of poorly soluble drugs. *Nanoparticulates as drug carriers*, 2006; 1: 307-28.
 22. Rabinow B, Kipp J, Papadopoulos P, Wong J, Glosson J, Gass J, Sun CS, Wielgos T, White R, Cook C, Barker K. Itraconazole IV nanosuspension enhances efficacy through altered pharmacokinetics in the rat. *Int. J. Pharm.*, 2007; 339(1-2): 251-60.
 23. Wang Y, Li X, Wang L, Xu Y, Cheng X, Wei P. Formulation and pharmacokinetic evaluation of a paclitaxel nanosuspension for intravenous delivery. *Int J Nanomedicine*, 2011: 1497-507.
 24. Talekar M, Kendall J, Denny W, Jamieson S, Garg S. Development and evaluation of PIK75 nanosuspension, a phosphatidylinositol-3-kinase inhibitor. *Eur J Pharm Sci.*, 2012; 47(5): 824-33.
 25. Gonzalez MA, Rigo MR, Vidal NG. Praziquantel systems with improved dissolution rate obtained by high pressure homogenization. *Mater. Sci. Eng. C.*, 2018; 93(3): 28-35.
 26. Trask AV, Jones W. Crystal engineering of organic cocrystals by the solid-state grinding approach. *Organic Solid-State Reactions*, 2005: 41-70.
 27. Braga D, Maini L, Grepioni F. Mechanochemical preparation of co-crystals. *Chem. Soc. Rev.*, 2013; 42(18): 7638-48.
 28. Jug M, Mura PA. Grinding as solvent-free green chemistry approach for cyclodextrin inclusion complex preparation in the solid state. *Pharmaceutics*, 2018; 10(4): 1-22.
 29. Liu M, Hong C, Li G, Ma P, Xie Y. The generation of myricetin–nicotinamide nanococrystals by top down and bottom-up technologies. *Nanotechnology*, 2016; 27(39): 1-9.
 30. Jones W, Motherwell WS, Trask AV. Pharmaceutical cocrystals: An emerging approach to physical property enhancement. *MRS bulletin*, 2006; 31(11): 875-9.
 31. Shan N, Toda F, Jones W. Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics. *Chem. Commun.*, 2002; 11(20): 2372-3.
 32. Emami S, Siah-Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. *BioImpacts: BI.*, 2018; 8(4): 305.
 33. Chung HR, Kwon E, Oikawa H, Kasai H, Nakanishi H. Effect of solvent on organic nanocrystal growth using the reprecipitation method. *J. Cryst. Growth*, 2006; 294(2): 459- 63.
 34. Vega-Mercado H, Góngora-Nieto MM, Barbosa-Cánovas GV. Advances in dehydration of foods. *J. Food Eng.*, 2001; 49(4): 271-89.
 35. Sosnik A, Seremeta KP. Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers. *Adv. Colloid Interface Sci.*, 2015; 223: 40-54.
 36. Alhalaweh A, Velaga SP. Formation of cocrystals from stoichiometric solutions of incongruently saturating systems by spray drying. *Crystal growth & design*, 2010; 10(8): 3302-5.
 37. Alhalaweh A, Kaialy W, Buckton G, Gill H,

- Nokhodchi A, Velaga SP. Theophylline cocrystals prepared by spray drying: physicochemical properties and aerosolization performance. *Aaps Pharmscitech.*, 2013; 14: 265-76.
38. Baba K, Nishida K. Calpain inhibitor nanocrystals prepared using Nano Spray Dryer B-90. *Nanoscale Res. Lett.*, 2012; 7(3): 1-9.
39. Prinn KB, Costantino HR, Tracy M. Statistical modeling of protein spray drying at the lab scale. *Aaps Pharmscitech.*, 2002; 3(2): 32-9.
40. Bevis J, Bottom R, Duncan J, Farhat I, Forrest M, Furniss D, MacNaughton B, Nazhat S, Saunders M, Seddon A. Principles and applications of thermal analysis. Wiley Online Library; 2008.
41. Höhne GW, Hemminger WF, Flammersheim HJ, Höhne GW, Hemminger WF, Flammersheim HJ. Theoretical fundamentals of differential scanning calorimeters. *Differential scanning calorimetry*, 2003; 31-63.
42. Lu J, Rohani S. Preparation and characterization of theophylline– nicotinamide cocrystal. *Organic Process Research & Development*, 2009; 13(6): 1269-75.
43. Stuart B. Infrared spectroscopy. *Analytical techniques in forensic science*, 2021; 145-60.
44. Guo M, Fu Q, Wu C, Guo Z, Li M, Sun J, He Z, Yang L. Rod shaped nanocrystals exhibit superior in vitro dissolution and in vivo bioavailability over spherical like nanocrystals: a case study of lovastatin. *Colloids and Surfaces B: Biointerfaces*, 2015; 128(4): 1-44.
45. Ricarte RG, Lodge TP, Hillmyer MA. Detection of pharmaceutical drug crystallites in solid dispersions by transmission electron microscopy. *Mol. Pharm.*, 2015; 12(3): 983-90.
46. Pinon AC, Rossini AJ, Widdifield CM, Gajan D, Emsley L. Polymorphs of theophylline characterized by DNP enhanced solid-state NMR. *Mol. Pharm.*, 2015; 12(11): 1-8.
47. Ali MR, Asha KF, Paul S, Rahman BM. Formulation Development and Evaluation of Poorly Water Soluble Gliclazide Tablet Containing Aerosil 380 as Carrier. *Pharmacology & Pharmacy*, 2019; 10(09): 396-5.
48. Uppal S, Italiya KS, Chitkara D, Mittal A. Nanoparticulate-based drug delivery systems for small molecule anti-diabetic drugs: An emerging paradigm for effective therapy. *Acta Biomaterialia*, 2018; 81(2): 20-42.
49. Sarkhel S, Shuvo SM, Ansari MA, Mondal S, Kapat P, Ghosh A, Sarkar T, Biswas R, Atanase LI, Carauleanu A. Nanotechnology-Based Approaches for the Management of Diabetes Mellitus: An Innovative Solution to Long-Lasting Challenges in Antidiabetic Drug Delivery. *Pharmaceutics*, 2024; 16(12): 1-28.