MICROBIOLOGY ARCHIVES
ReviewArticle | ISSN: 3041-590X
Journal homepage: https://microjournal.researchfloor.org/

Improving Physicochemical Characteristics of Pharmaceuticals through Microbe and Cocrystal Synergy

Sushila*

Department of Pharmaceutical Sciences, Lord's University, Alwar, Rajasthan 301028, India

ARTICLE INFO

Citation: Sushila (2023). Improving Physicochemical Characteristics of Pharmaceuticals through Microbe and Cocrystal Synergy.
Microbiology Archives, an International Journal.
DOI: https://doi.org/10.51470/MA.2023.5.2.14

Received 12 July 2023
Revised 17 August 2023
Accepted 18 September 2023
Available Online October 20 2023

Corresponding Author: **Sushila**
E-Mail: **siradhana13@gmail.com**

ABSTRACT

Pharmaceutical cocrystals have emerged as a transformative strategy for enhancing the physicochemical properties of active pharmaceutical ingredients (APIs), including solubility, dissolution rate, thermal stability, and mechanical behavior, without altering their molecular integrity. In parallel, microbial systems have demonstrated significant potential in drug development, particularly through biotransformation processes that improve drug selectivity, reduce toxicity, and enhance bioavailability. Recent advances suggest that the integration of microbial technology with cocrystal engineering could offer a synergistic platform for the design of more effective and sustainable drug formulations. This interdisciplinary approach leverages the metabolic diversity of microbes to produce or modify pharmaceutical compounds, which can subsequently be engineered into cocrystals to achieve desired pharmacokinetic and pharmacodynamic profiles. The combination of environmentally benign microbial processes with crystal design principles provides an innovative avenue for tailoring drug properties to meet therapeutic and regulatory demands. This article reviews the current progress in both microbial-assisted drug modification and pharmaceutical cocrystallization and highlights their convergence as a promising frontier in pharmaceutical research. By uniting microbiology, materials science, and pharmaceutical chemistry, this strategy holds significant promise for the development of next-generation pharmaceuticals with improved efficacy, safety, and environmental sustainability

Keywords: *pharmaceutical cocrystals, microbes, physicochemical properties, drug solubility, biotransformation, drug delivery*

1. Introduction

The pharmaceutical industry continues to grapple with a significant challenge: the limited solubility and bioavailability of many active pharmaceutical ingredients (APIs). Despite advances in drug discovery, a large proportion of new chemical entities (NCEs) identified through high-throughput screening techniques exhibit poor aqueous solubility and low membrane permeability. These limitations can compromise oral absorption, therapeutic efficacy, and ultimately, clinical success. Enhancing the physicochemical characteristics of these drugs remains a critical goal in formulation science [1]. Traditional strategies such as salt formation, particle size reduction (micronization), solid dispersions, and lipid-based systems have been widely employed to address solubility and stability challenges. However, these approaches often present issues such as chemical instability, high production costs, process complexity, and limited applicability to non-ionizable or poorly crystalline drugs [2]. For instance, salt formation is restricted to ionizable compounds, while micronization may lead to aggregation and poor flow properties. These shortcomings have spurred interest in alternative methods to improve drug performance without compromising structural integrity. One such emerging strategy is the use of pharmaceutical cocrystals. Cocrystals are defined as multicomponent crystalline solids formed between an API and a pharmaceutically acceptable coformer, linked by non-covalent interactions such as hydrogen bonding, π-π stacking, or van der Waals forces. Unlike salts, cocrystals do not involve ionic interactions and therefore are applicable to a broader range of APIs [3]. Moreover, they can be designed to enhance a variety of properties, including solubility, dissolution rate, mechanical compressibility, stability, and even taste masking, all while maintaining the pharmacological activity of the parent molecule.

Cocrystal engineering draws upon principles from supramolecular chemistry and crystal design, allowing formulation scientists to selectively manipulate crystal packing and intermolecular interactions. Numerous studies have demonstrated improved in vivo performance of cocrystallized APIs, including enhanced absorption and bioavailability. Importantly, cocrystals are also increasingly recognized by regulatory agencies such as the FDA and EMA, making them a viable and scalable strategy for commercial drug development [4]. In parallel to advancements in crystal engineering, microbial biotechnology has gained momentum in the pharmaceutical sciences. Microbes, particularly bacteria and fungi, possess diverse enzymatic systems capable of catalyzing complex chemical transformations under mild and environmentally friendly conditions. Biocatalysis using microbial strains or isolated enzymes enables regioselective and stereoselective modifications of APIs or intermediates, facilitating the synthesis of active metabolites or more bioavailable drug analogs.

Microbial systems have been successfully utilized in the production of steroids, antibiotics, alkaloids, and anti-inflammatory agents, among others [5]. Microbial processes also offer sustainability advantages, including reduced reliance on toxic reagents and solvents, lower energy consumption, and minimized waste generation. The versatility of microbes in transforming a wide range of substrates, coupled with their adaptability through genetic engineering, makes them ideal tools for green pharmaceutical development. Furthermore, certain microbial metabolites or fermentation products can serve as potential coformers in cocrystal formation, thereby expanding the scope of both disciplines.

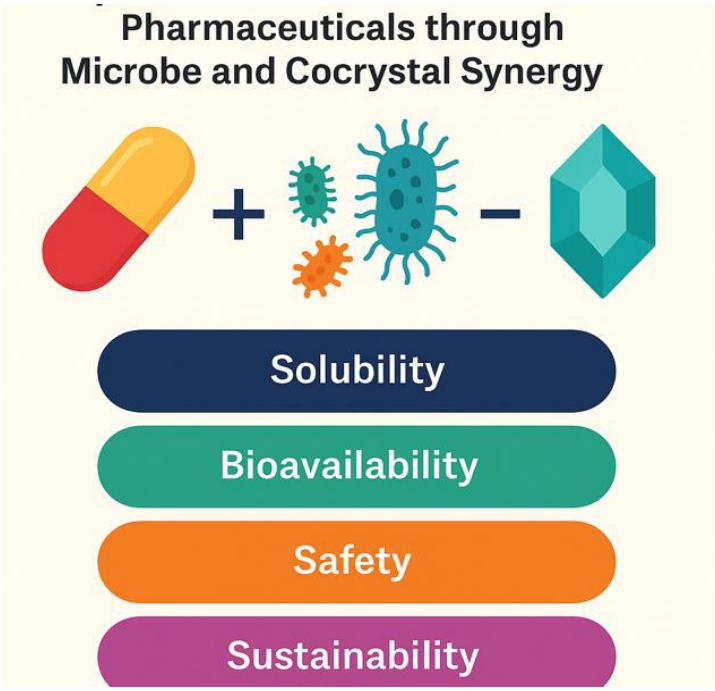

Fig 1. This fig illustrates how microbial transformation and pharmaceutical cocrystals work together to enhance drug properties

The convergence of cocrystal engineering and microbial technology represents an exciting interdisciplinary frontier. Combining the specificity and eco-friendliness of microbial transformations with the design flexibility of cocrystals could lead to novel formulations with superior therapeutic and environmental profiles [6]. For instance, microbial biotransformation could be employed to modify poorly soluble APIs into more hydrophilic intermediates, which can subsequently be cocrystallized with appropriate coformers to further enhance their stability and delivery [7]. Alternatively, naturally derived microbial metabolites could be explored as functional coformers with added pharmacological or nutraceutical benefits. Moreover, microbial-assisted crystallization processes are being investigated to facilitate selective nucleation and control polymorphism, both of which are critical factors in drug development [8]. This integrative approach not only broadens the formulation toolbox but also aligns with the growing emphasis on sustainable, cost-effective, and patient-centric pharmaceutical innovation, the current state of pharmaceutical cocrystals and microbial applications in drug formulation, and propose a synergistic strategy that leverages the strengths of both fields. By reviewing recent developments, challenges, and potential pathways for integration, we aim to shed light on a promising direction for the development of next-generation drug delivery systems.

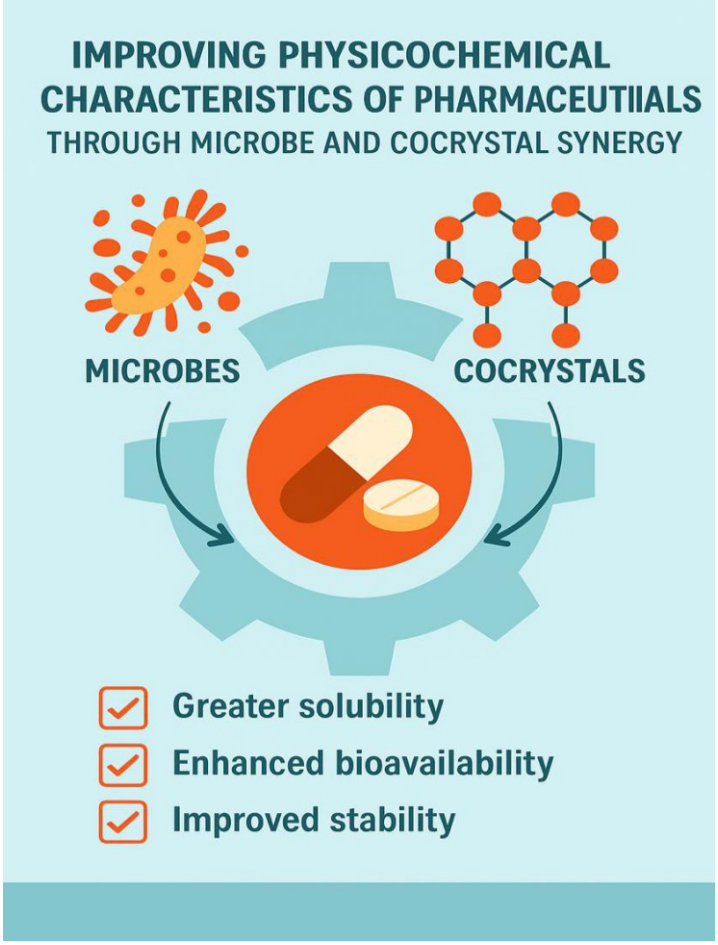

Fig 2. This image presents a clean, flat-design digital infographic depicting the synergistic enhancement of pharmaceutical properties through microbial transformation and cocrystal technology. It visually connects microbial agents and bioactive metabolites with crystalline drug structures, emphasizing improvements in solubility, stability, and bioavailability.

2. Pharmaceutical Cocrystals: An Overview

Pharmaceutical cocrystals represent a versatile and scientifically validated approach to modifying the physicochemical properties of active pharmaceutical ingredients (APIs) without altering their intrinsic pharmacological activity. Unlike traditional salt formation, which is limited to ionizable compounds, cocrystals are formed by the non-covalent association of an API with one or more coformers in a fixed stoichiometric ratio [9]. These interactions, typically hydrogen bonds, π–π stacking, or van der Waals forces, allow for fine-tuning of the drug's solid-state characteristics while preserving its molecular identity. Cocrystallization enables the systematic engineering of key properties such as aqueous solubility, dissolution rate, mechanical compressibility, hygroscopicity, thermal stability, and even organoleptic properties [10]. As poor solubility and bioavailability continue to hinder the development of many promising drug candidates, cocrystals offer a practical solution to improve in vivo performance without the need for chemical modification.

The selection of suitable coformers is a critical aspect of successful cocrystal design. Ideal coformers are generally pharmaceutically acceptable substances with well-characterized safety profiles—many of which are classified under the U.S. FDA's Generally Recognized As Safe (GRAS) category.

Coformers must also possess functional groups capable of forming reliable and reproducible intermolecular interactions with the API [11]. In addition to conventional excipients, coformers may include nutraceuticals, organic acids, bases, amino acids, or even other APIs, leading to the potential for dual-drug cocrystals with synergistic therapeutic effects.

Several well-documented examples illustrate the practical utility of cocrystallization. For instance, carbamazepine-saccharin cocrystals demonstrate significantly enhanced dissolution rates and reduced polymorphic variability compared to carbamazepine alone. Similarly, fluoxetine-benzoic acid cocrystals exhibit improved solubility and oral bioavailability, offering a promising route for enhanced drug delivery in antidepressant therapy [12]. These case studies highlight how rational cocrystal design can bridge the gap between chemical structure and formulation performance. The preparation of pharmaceutical cocrystals can be achieved using a variety of techniques, broadly categorized into solvent-based and solid-state methods. Solvent evaporation, slow solvent cooling, and slurry conversion are commonly employed in laboratory and pilot-scale settings due to their simplicity and scalability. Neat grinding and liquid-assisted grinding (LAG) are popular mechanochemical approaches that eliminate or minimize solvent use, aligning with green chemistry principles [13]. More advanced techniques such as supercritical fluid crystallization, hot melt extrusion, and spray drying are increasingly being explored for continuous and industrial-scale production. Regardless of the synthesis method, accurate characterization of cocrystals is essential to confirm their identity, purity, and stability. Analytical techniques routinely employed include:

- **Powder X-ray diffraction (PXRD)**: The gold standard for phase identification and confirmation of unique crystal structures.
- **Differential scanning calorimetry (DSC)** and **thermogravimetric analysis (TGA)**: Used to assess thermal behavior, melting points, and potential polymorphic transitions.
- **Fourier-transform infrared spectroscopy (FTIR)** and **Raman spectroscopy**: Applied to detect changes in functional group environments and confirm hydrogen bonding patterns.
- **Solid-state nuclear magnetic resonance (ssNMR)** and **single-crystal X-ray diffraction (SCXRD)**: Utilized for in-depth structural elucidation and molecular arrangement within the crystal lattice.

In vitro dissolution studies, mechanical stress testing, and accelerated stability assays are employed to assess the pharmaceutical suitability of cocrystal formulations under real-world conditions. As regulatory frameworks continue to evolve, pharmaceutical cocrystals are gaining increasing acceptance [14]. The U.S. FDA recognizes cocrystals as distinct solid forms of APIs, provided they exhibit consistent physicochemical profiles and do not dissociate under normal conditions. This growing regulatory clarity has encouraged further research and commercialization of cocrystal-based drug products, pharmaceutical cocrystals serve as a powerful platform to address long-standing formulation challenges [15]. Their ability to enhance solubility, stability, and bioavailability without altering the drug's therapeutic profile makes them highly attractive for modern drug development. When coupled with biotechnological innovations—such as microbial transformations—cocrystals hold even greater potential for creating next-generation pharmaceutical products.

3. Microbial Transformation in Drug Development

Microbial transformation, also known as microbial biotransformation, has emerged as a vital strategy in pharmaceutical research for the structural modification of bioactive compounds. This process involves the use of microorganisms—predominantly fungi, bacteria, and actinomycetes—to carry out specific chemical reactions that are often challenging to achieve through conventional synthetic methods. These transformations occur under environmentally benign conditions, offering a green, cost-effective, and highly selective alternative to traditional organic synthesis, an advantages of microbial transformation is its ability to catalyze complex, regio- and stereoselective modifications without the need for harsh reagents or extreme processing conditions. Among the most commonly observed reactions facilitated by microbial enzymes are hydroxylation, oxidation, reduction, glycosylation, methylation, acetylation, and dealkylation [16]. Such modifications can significantly influence the physicochemical and pharmacological properties of parent drug molecules, including enhanced aqueous solubility, improved membrane permeability, reduced toxicity, and increased metabolic stability.

Hydroxylation, for instance, is frequently employed to increase the hydrophilicity and bioavailability of hydrophobic drugs. Microbial glycosylation can render lipophilic compounds more water-soluble, thereby improving their absorption and therapeutic index. In many cases, microbial transformation results in the generation of active metabolites that exhibit superior bioactivity or lower side-effect profiles compared to the original compound. These derivatives may also act as scaffolds or intermediates for further synthetic development. A wide range of microbial species has been exploited for drug biotransformation due to their diverse enzymatic capabilities. Streptomyces species, known for their prolific secondary metabolism, have been extensively studied for the bioconversion of steroids, alkaloids, and antibiotics [17]. Similarly, Cunninghamella elegans, a filamentous fungus, mimics mammalian metabolism and is commonly used to predict phase I drug metabolites. Its ability to hydroxylate aromatic rings, oxidize heteroatoms, and introduce polar functional groups makes it a model organism in pharmacokinetic studies. Other notable examples include *Aspergillus niger*, *Rhizopus spp.*, *Nocardia spp.*, and *Bacillus spp.*, each offering unique enzyme systems capable of specific biotransformations. These microbes can be cultivated under defined conditions, and their enzyme expression can be manipulated or enhanced through genetic engineering, cofactor supplementation, or metabolic pathway optimization, microbial transformations are not limited to improving existing drugs; they also play a crucial role in natural product drug discovery, where microorganisms can modify plant-derived compounds into novel derivatives with enhanced therapeutic properties [18]. This microbial-driven diversification of molecular structures supports the development of drug candidates with optimized pharmacokinetic and pharmacodynamic profiles, microbial transformation can intersect with cocrystal technology in meaningful ways. Certain microbial metabolites can serve as coformers in cocrystallization processes, contributing not only to the solid-state modulation of the drug but also offering additional biological benefits such as antioxidant, anti-inflammatory, or antimicrobial activity. For instance, biotransformed flavonoids or phenolic acids may act as both functional excipients and pharmacologically active coformers, enabling dual-function

cocrystals with enhanced performance, microbial processes may even be used to generate prodrugs or intermediate compounds that are later crystallized with coformers to form advanced solid formulations. This integrated approach aligns with current trends in green chemistry and sustainable pharmaceutical manufacturing, promoting safer, more efficient, and environmentally responsible drug development pipelines, microbial transformation offers a powerful platform for modifying pharmaceutical compounds with high specificity and under eco-friendly conditions [19]. Its synergy with cocrystal engineering holds substantial promise for the creation of novel drug formulations that are not only effective but also environmentally sustainable. As our understanding of microbial metabolism and enzymatic pathways deepens, so too does the potential for developing innovative drug delivery systems that harness the best of both microbiology and material science.

Table 1: Comparison of Traditional Formulation Techniques vs. Cocrystallization

Parameter	Salt Formation	Micronization	Encapsulation	Cocrystallization
Molecular Modification	Yes	No	No	No
Solubility Enhancement	Moderate	Moderate	Low to Moderate	High
Stability Improvement	Low	Low	High	High
Regulatory Complexity	Medium	Low	High	Low to Medium
Industrial Scalability	High	High	Medium	Medium to High

Table 2: Examples of Microbial Metabolites Used as Pharmaceutical Coformers

Microbial Metabolite	Microbial Source	Pharmaceutical Use	Potential in Cocrystals
Succinic Acid	*Escherichia coli*, *Aspergillus spp.*	Solubility enhancer	Coformer with antifungal drugs
Citric Acid	*Aspergillus niger*	Preservative, pH adjuster	Coformer for enhancing dissolution
Kojic Acid	*Aspergillus oryzae*	Skin-lightening agent	Coformer with antibacterial drugs
Ferulic Acid	*Streptomyces spp.*	Antioxidant	Dual activity + cocrystal role

Table 3: Benefits of Microbe-Cocrystal Synergy in Drug Formulation

Attribute	Microbial Transformation	Cocrystallization	Synergistic Benefit
Solubility	Enhanced via hydroxylation, etc.	Improved by crystal lattice design	Maximal solubility and dissolution
Bioavailability	Biotransformed metabolites absorbed better	Controlled release possible	Enhanced oral bioavailability
Safety and Biocompatibility	Natural metabolites usually safe	GRAS coformers used	Improved safety profiles
Sustainability	Green, low-waste processes	Solvent-free or low-energy routes	Eco-friendly formulation pipeline

Table 4: Techniques for Synthesis and Characterization of Cocrystals

Technique	Purpose	Relevance
Solvent Evaporation	Slow co-crystal formation	Precise crystal control
Neat Grinding	Mechanochemical synthesis	Solvent-free, eco-friendly
PXRD (X-Ray Diffraction)	Crystal structure determination	Confirms cocrystal formation
DSC (Differential Scanning Calorimetry)	Thermal behavior analysis	Stability assessment
FT-IR Spectroscopy	Functional group identification	Coformer-API interaction tracking

4. Synergistic Approach: Microbes and Cocrystals

The integration of microbial transformation with pharmaceutical cocrystal engineering represents an emerging and highly promising strategy to overcome long-standing challenges in drug formulation. This synergistic approach leverages the unique strengths of microbial biotechnology—such as regioselective modification and eco-friendly synthesis—and the solid-state modulation capabilities of cocrystallization to develop pharmaceutical products with superior physicochemical and therapeutic profiles [20]. There are several key dimensions through which microbes and cocrystals can be effectively combined in a pharmaceutical context:

a) Microbial Metabolites as Coformers

One of the most direct points of convergence is the use of microbial metabolites as natural coformers in cocrystal design. Compounds such as citric acid, fumaric acid, kojic acid, lactic acid, and other secondary metabolites produced by microorganisms possess favorable characteristics for cocrystal formation, including the presence of multiple hydrogen-bond donor or acceptor groups and Generally Recognized as Safe (GRAS) status [21]. These bio-based coformers not only enhance the solubility and dissolution rates of poorly soluble active pharmaceutical ingredients (APIs) but also often confer additional pharmacological properties, such as antioxidant, antimicrobial, or anti-inflammatory effects. The use of such multifunctional coformers can result in dual-action pharmaceutical cocrystals, where both the API and coformer contribute to the overall therapeutic activity.

b) Microbial Pre-Treatment of APIs

Microbial transformation can be strategically employed to modify APIs prior to the cocrystallization step. Through selective hydroxylation, oxidation, or functionalization, microbial biocatalysts can introduce polar functional groups—such as hydroxyl, carboxyl, or amine groups—onto the drug molecule [22]. These modifications improve the API's capacity to engage in hydrogen bonding or other supramolecular interactions essential for robust cocrystal formation. For example, an API that is initially hydrophobic and lacks suitable binding sites for cocrystal synthesis may be converted by microbial enzymes into a more hydrophilic derivative with enhanced cocrystallization potential. This pre-treatment not only broadens the range of coformers that can be used but also contributes to improved solubility, wettability, and oral bioavailability.

c) Biogenic or Microbe-Assisted Synthesis of Cocrystals

In addition to serving as sources of coformers or modifying agents, microorganisms may play a more direct role in the synthesis of cocrystals through bioinspired or bioassisted processes. Certain microbes are capable of inducing mineralization or biomolecular self-assembly, which can be harnessed to facilitate environmentally friendly or solvent-free cocrystal formation. These processes may involve the secretion of metabolites that act as nucleation agents or pH modifiers to create favorable conditions for solid-state assembly [23]. Although this area is still underexplored, it offers substantial potential for the development of scalable, green chemistry

protocols for cocrystal production, minimizing the use of organic solvents and energy-intensive processes.

d) Combined Benefits and Future Potential

The hybrid application of microbial transformation and cocrystal engineering holds immense potential for tailoring the pharmacokinetics and pharmacodynamics of drug molecules. Cocrystals formed using microbially transformed APIs or natural microbial coformers can exhibit:

- Improved dissolution rates and aqueous solubility
- Enhanced physical and chemical stability
- Modified drug release profiles (e.g., sustained or targeted release)
- Reduced excipient load and improved patient compliance
- Dual or synergistic therapeutic effects

This interdisciplinary approach aligns with current trends in sustainable pharmaceutical development. It promotes reduced reliance on synthetic reagents, lowers production costs, and complies with green chemistry principles [24]. The combination of microbial precision and crystal design versatility also allows for the customization of drug formulations based on patient-specific or disease-specific needs, the synergy between microbial biotechnology and pharmaceutical cocrystallization is a powerful, multifaceted strategy for addressing formulation challenges in modern drug development. By integrating these domains, researchers can unlock new pathways for the design of advanced pharmaceutical solids that are not only efficacious and bioavailable but also safer and more environmentally responsible. Future efforts should focus on standardizing microbial-cocrystal workflows, identifying new microbial strains and metabolites suitable for cocrystal applications, and evaluating the long-term stability and clinical performance of such formulations.

5. Applications and Case Studies

The integration of microbial biotechnology with pharmaceutical cocrystallization has opened up promising avenues for drug formulation and delivery. One notable example involves the use of succinic acid, a metabolite derived from microbial fermentation, as a coformer in the development of fluconazole cocrystals. This combination resulted in enhanced solubility, improved dissolution rate, and superior antifungal efficacy compared to the parent drug. The naturally derived coformer not only contributed to the physicochemical improvement of the active pharmaceutical ingredient (API) but also ensured better biocompatibility and sustainability [25]. Such applications are especially significant for Biopharmaceutical Classification System (BCS) Class II drugs, which are characterized by low solubility and high permeability. By forming cocrystals with microbial coformers, these drugs can overcome solubility limitations, leading to improved oral bioavailability without the need for complex excipient-based formulations, cocrystal formation has shown potential in mitigating food effects on drug absorption [26]. By stabilizing the drug in a more soluble crystalline phase, fluctuations in gastrointestinal conditions are less likely to impact the pharmacokinetics of the API, microbial coformers with inherent pharmacological activity offer a unique opportunity to develop dual-function therapeutics [27]. For instance, metabolites such as citric acid and ferulic acid possess antioxidant, antimicrobial, or anti-inflammatory properties. When used as coformers, these compounds can synergize with the API, resulting in cocrystals that not only improve bioavailability but also enhance therapeutic outcomes through complementary biological mechanisms. Emerging case studies continue to support the feasibility of microbial-metabolite-based cocrystals in addressing formulation challenges for poorly water-soluble drugs, suggesting a sustainable and multifunctional approach for next-generation pharmaceuticals.

6. Challenges and Future Perspectives

While the integration of microbial biotransformation and pharmaceutical cocrystallization presents a novel and potentially transformative strategy, several challenges must be addressed to facilitate its widespread adoption and scalability. One of the foremost barriers is the regulatory complexity surrounding the use of microbial-derived coformers. Although many microbial metabolites (such as citric acid or succinic acid) are recognized as safe by regulatory agencies like the U.S. FDA and EFSA, the introduction of new or modified metabolites raises concerns about toxicity, immunogenicity, and consistency [28]. Establishing regulatory pathways for novel microbial coformers will require rigorous safety assessments and comprehensive toxicological data to ensure patient safety and therapeutic efficacy, the challenge lies in the scalability and reproducibility of microbial transformations [34]. While microbial processes offer environmental and economic advantages, they are often sensitive to changes in culture conditions, substrate availability, and strain stability. Ensuring uniform production of desired metabolites at an industrial scale demands the development of robust fermentation protocols and strain engineering techniques. Furthermore, the variability of biological systems poses a risk to batch-to-batch consistency, which is a critical parameter in pharmaceutical manufacturing, there are technical limitations in integrating microbial products with current cocrystal synthesis techniques. The compatibility of microbial coformers with established methods like solvent evaporation, mechanochemical synthesis, and supercritical fluid crystallization must be evaluated. Issues such as coformer stability, hygroscopicity, and the potential for microbial contamination must be carefully managed to ensure process feasibility and product purity, future research should focus on several key areas to overcome these challenges [29]. First, the systematic identification and characterization of novel microbial strains capable of producing pharmaceutically relevant metabolites will expand the pool of available coformers [33]. This effort can be supported by advances in metagenomics and microbial ecology, which enable the exploration of previously untapped microbial biodiversity in various ecosystems, there is a growing opportunity to leverage systems biology and metabolic engineering to design microbes with optimized pathways for producing specific coformers with high yield and purity [30]. AI-driven predictive modeling can be employed to understand the physicochemical interactions between APIs and microbial metabolites, facilitating the rational selection of compatible coformer candidates and guiding experimental designs, the interdisciplinary collaboration between pharmaceutical scientists, microbiologists, regulatory experts, and process engineers will be crucial to translating this concept from the laboratory to commercial application [31-32]. Development of standardized protocols and best practices for microbial-coformer selection, characterization, and regulatory evaluation will accelerate adoption, while there are technical and regulatory hurdles to overcome, the synergy between microbial biotransformation

and pharmaceutical cocrystallization holds vast potential. With continued innovation and collaboration, this strategy may pave the way for the next generation of sustainable, high-performance drug formulations that meet the needs of modern medicine.

7. Conclusion

The convergence of microbial biotransformation and pharmaceutical cocrystallization offers a promising frontier in modern drug formulation and delivery. This integrated strategy addresses several longstanding challenges in pharmaceutical sciences, particularly the poor solubility, low bioavailability, and limited therapeutic efficacy that afflict many active pharmaceutical ingredients (APIs). By leveraging the unique metabolic capabilities of microbes to produce bioactive or solubility-enhancing coformers, and coupling these with the structural precision of cocrystal engineering, researchers can create advanced drug forms with tailored physicochemical and pharmacokinetic profiles. This synergy enables not only improved drug performance but also contributes to the growing demand for environmentally friendly and sustainable pharmaceutical manufacturing practices. Microbial processes are typically low-energy, selective, and scalable, while cocrystals can be engineered using green chemistry principles, reducing reliance on hazardous solvents and resource-intensive processing steps, the pathway toward practical implementation is not without obstacles. Regulatory validation, large-scale reproducibility, and comprehensive safety assessments of microbial-derived coformers remain critical challenges that must be systematically addressed. Interdisciplinary collaboration—bringing together expertise from microbiology, crystal engineering, pharmaceutical sciences, and regulatory affairs—will be essential for bridging the gap between laboratory feasibility and real-world application, the novel microbial strains and coformers are identified, the development of intelligent, patient-centric drug delivery systems will become increasingly achievable. With the aid of tools such as artificial intelligence, systems biology, and high-throughput screening, the integration of microbial and cocrystal technologies may revolutionize the pharmaceutical landscape, leading to a new generation of safe, effective, and sustainable therapeutics that better serve global healthcare needs.

References

1. Ngilirabanga, J. B., & Samsodien, H. (2021). Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy. *Nano Select*, *2*(3), 512-526.

2. Guan, D., Xuan, B., Wang, C., Long, R., Jiang, Y., Mao, L., ... & Zhou, Q. (2021). Improving the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients derived from traditional Chinese medicine through cocrystal engineering. *Pharmaceutics*, *13*(12), 2160.

3. Yadav, A. V., Shete, A. S., Dabke, A. P., Kulkarni, P. V., & Sakhare, S. S. (2009). Co-crystals: a novel approach to modify physicochemical properties of active pharmaceutical ingredients. *Indian journal of pharmaceutical sciences*, *71*(4), 359.

4. Majodina, S., Ndima, L., Abosede, O. O., Hosten, E. C., Lorentino, C. M., Frota, H. F., & Ogunlaja, A. S. (2021). Physical stability enhancement and antimicrobial properties of a sodium ionic cocrystal with theophylline. *CrystEngComm*, *23*(2), 335-352.

5. Islam, N. U., Umar, M. N., Khan, E., Al-Joufi, F. A., Abed, S. N., Said, M., & Khan, F. A. (2022). Levofloxacin cocrystal/salt with phthalimide and caffeic acid as promising solid-state approach to improve antimicrobial efficiency. *Antibiotics*, *11*(6), 797.

6. Pan, X., Zheng, Y., Chen, R., Qiu, S., Chen, Z., Rao, W., .& Guan, X. (2019). Cocrystal of sulfamethazine and p-aminobenzoic acid: structural establishment and enhanced antibacterial properties. *Crystal Growth & Design*, *19*(4), 2455-2460.

7. Wang, L. Y., Zhao, M. Y., Bu, F. Z., Niu, Y. Y., Yu, Y. M., Li, Y. T., & Wu, Z. Y. (2021). Cocrystallization of amantadine hydrochloride with resveratrol: the first drug–nutraceutical cocrystal displaying synergistic antiviral activity. *Crystal Growth & Design*, *21*(5), 2763-2776.

8. Meng, S. S., Yu, Y. M., Bu, F. Z., Yan, C. W., Wu, Z. Y., & Li, Y. T. (2022). Directional Self-Assembly of Ofloxacin and Syringic Acid: The First Salt Cocrystal of Ofloxacin with Phenolic Acid Displays Superior In V itro/Vivo Biopharmaceutical Property and Enhanced Antibacterial Activity. *Crystal Growth & Design*, *22*(11), 6735-6750.

9. Al-Dulaimi, A. F., Al-kotaji, M., & Abachi, F. T. (2022). Co-crystals for improving solubility and bioavailability of pharmaceutical products. *Egyptian Journal of Chemistry*, *65*(1), 81-89.

10. Thakuria, R., & Sarma, B. (2018). Drug-drug and drug-nutraceutical cocrystal/salt as alternative medicine for combination therapy: a crystal engineering approach. *Crystals*, *8*(2), 101.

11. Singh, M., Barua, H., Jyothi, V. G. S., Dhondale, M. R., Nambiar, A. G., Agrawal, A. K., & Kumar, D. (2023). Cocrystals by design: a rational coformer selection approach for tackling the API problems. *Pharmaceutics*, *15*(4), 1161.

12. Nugrahani, I., & Parwati, R. D. (2021). Challenges and progress in nonsteroidal anti-inflammatory drugs co-crystal development. *Molecules*, *26*(14), 4185.

13. Maity, D. K., Paul, R. K., & Desiraju, G. R. (2020). Drug–drug binary solids of nitrofurantoin and trimethoprim: crystal engineering and pharmaceutical properties. *Molecular Pharmaceutics*, *17*(12), 4435-4442.

14. Deng, Y., Deng, W., Huang, W., Zheng, Z., Zhang, R., Liu, S., & Jiang, Y. (2022). Norfloxacin co-amorphous salt systems: Effects of molecular descriptors on the formation and physical stability of co-amorphous systems. *Chemical Engineering Science*, *253*, 117549.

15. Devi, S., Kumar, A., Kapoor, A., Verma, V., Yadav, S., & Bhatia, M. (2022). Ketoprofen–FA co-crystal: in vitro and in vivo investigation for the solubility enhancement of drug by design of expert. *AAPS PharmSciTech*, *23*(4), 101.

16. Yu, Y. M., Yu, M. C., Wang, L. Y., Li, Y. T., Wu, Z. Y., & Yan, C. W. (2020). A supramolecular adduct of tegafur and syringic acid: the first tegafur-nutraceutical cocrystal with perfected in vitro and in vivo characteristics as well as synergized anticancer activities. *New Journal of Chemistry*, *44*(37), 15994-16005.

17. Yu, Y. M., Yu, M. C., Wang, L. Y., Li, Y. T., Wu, Z. Y., & Yan, C. W. (2020). A supramolecular adduct of tegafur and syringic acid: the first tegafur-nutraceutical cocrystal with perfected in vitro and in vivo characteristics as well as synergized anticancer activities. *New Journal of Chemistry*, *44*(37), 15994-16005.

18. Karimi-Jafari, M., Ziaee, A., O'Reilly, E., Croker, D., & Walker, G. (2022). Formation of ciprofloxacin–isonicotinic acid cocrystal using mechanochemical synthesis routes—an investigation into critical process parameters. *Pharmaceutics*, *14*(3), 634.

19. Gopi, S. P., Ganguly, S., & Desiraju, G. R. (2016). A drug–drug salt hydrate of norfloxacin and sulfathiazole: enhancement of in vitro biological properties via improved physicochemical properties. *Molecular pharmaceutics*, *13*(10), 3590-3594.

20. Chakraborty, I., Ray, S., & Sahoo, P. (2023). Way of administrating supramolecular drug associates against multidrug-resistant bacteria in improving multidrug therapy. *Engineered Science*, *24*(2), 889.

21. Martin, F., Pop, M., Kacso, I., Grosu, I. G., Miclăuș, M., Vodnar, D., & Bâldea, I. (2020). Ketoconazole-p-aminobenzoic acid cocrystal: revival of an old drug by crystal engineering. *Molecular pharmaceutics*, *17*(3), 919-932.

22. Bianchi, F., Fornari, F., Riboni, N., Spadini, C., Cabassi, C. S., Iannarelli, M., & Careri, M. (2021). Development of novel cocrystal-based active food packaging by a quality by design approach. *Food Chemistry*, *347*, 129051.

23. Brunaugh, A. D., Sharma, S., & Smyth, H. (2021). Inhaled fixed-dose combination powders for the treatment of respiratory infections. *Expert opinion on drug delivery*, *18*(8), 1101-1115.

24. Serrano, D. R., Persoons, T., D'Arcy, D. M., Galiana, C., Dea-Ayuela, M. A., & Healy, A. M. (2016). Modelling and shadowgraph imaging of cocrystal dissolution and assessment of in vitro antimicrobial activity for sulfadimidine/4-aminosalicylic acid cocrystals. *European Journal of Pharmaceutical Sciences*, *89*, 125-136.

25. Wong, S. N., Chen, Y. C. S., Xuan, B., Sun, C. C., & Chow, S. F. (2021). Cocrystal engineering of pharmaceutical solids: Therapeutic potential and challenges. *CrystEngComm*, *23*(40), 7005-7038.

26. Makuvara, Z. (2022). Co-Crystallization of Plant-Derived Antimalarial Drugs: An Alternate Technique for Improved Physicochemical Qualities and Antimalarial Drug Synergy. In *Drug Formulation Design*. IntechOpen.

27. Al-Obaidi, H., Granger, A., Hibbard, T., & Opesanwo, S. (2021). Pulmonary drug delivery of antimicrobials and anticancer drugs using solid dispersions. *Pharmaceutics*, *13*(7), 1056.

28. Gu, W., Liu, D., & Sun, J. (2022). Co-crystallization of curcumin for improved photodynamic inactivation of Vibrio parahaemolyticus and its application for the preservation of cooked clams. *International journal of food microbiology*, *378*, 109816.

29. Qu, H., Li, Z., Wu, S., & Gong, J. (2023). Mechanosynthesis of magnolol multicomponent crystalline solids for improved natural antibiotics and customizable release profiles. *International Journal of Pharmaceutics*, *632*, 122530.

30. Sobierajska, P., Serwotka-Suszczak, A., Targonska, S., Szymanski, D., Marycz, K., & Wiglusz, R. J. (2022). Synergistic effect of toceranib and nanohydroxyapatite as a drug delivery platform—physicochemical properties and in vitro studies on mastocytoma cells. *International Journal of Molecular Sciences*, *23*(4), 1944.

31. Zhang, Y. X., Wang, L. Y., Dai, J. K., Liu, F., Li, Y. T., Wu, Z. Y., & Yan, C. W. (2019). The comparative study of cocrystal/salt in simultaneously improving solubility and permeability of acetazolamide. *Journal of Molecular Structure*, *1184*, 225-232.

32. Qu, H., Wu, S., & Gong, J. (2023). A sustainable and smart fungicide release platform through cocrystal nanocapsules for improved utilization rate and environmental safety. *Chemical Engineering Journal*, *473*, 145284.

33. Aziz, D. M., Hassan, S. A., Amin, A. A. M., Qurbani, K., & Aziz, S. B. (2023). A synergistic investigation of azo-thiazole derivatives incorporating thiazole moieties: a comprehensive exploration of their synthesis, characterization, computational insights, solvatochromism, and multimodal biological activity assessment. *RSC advances*, *13*(49), 34534-34555.

34. Kim, D. W., & Weon, K. Y. (2021). Pharmaceutical application and development of fixed-dose combination: Dosage form review. *Journal of Pharmaceutical Investigation*, *51*(5), 555-570.