Nano-Co-crystals: Engineering Precision Drug Delivery through Hybrid Crystal Nanotechnology

Nitin B. Kohale[1], Mayur S. Tekade[1*], Gajanan M. Jawalkar[1], Akash S. Jumble[1], Amitkumar P. Bodkhe[1], Umesh R. Bansod[1], Harigopal S. Sawarkar[1]

[1]Dr. Rajendra Gode College of Pharmacy, Amravati, Affiliated to Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad, Maharashtra, India

*Corresponding Author- Mayur Sanjay Tekade

Email Id- mayurtekade99@gmail.com / 8830278246

Dr. Rajendra Gode College of Pharmacy, Amravati, Affiliated to Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad, Maharashtra, India

Abstract

Nano-co-crystals have become a revolutionary pharmaceutical platform that combines the advantages of crystal engineering and nanotechnology to overcome the limitations of traditional drug delivery methods. Nano-co-crystals are formed by the combination of active pharmaceutical ingredients (APIs) with pharmaceutically acceptable co-formers in nano-scale crystalline architectures. These nano-co-crystals significantly improve the solubility, dissolution rate, bioavailability, physicochemical stability, and therapeutic performance of poorly water-soluble drugs. In recent years, surface functionalization, ligand-mediated targeting, stimuli-responsive behavior and incorporation with multifunctional nano-carriers have been developed to improve biopharmaceutical properties and hold promise as precision systems for drug delivery. These advances enable site-specific drug accumulation, controlled release and reduced systemic toxicity, expanding their application in cancer therapy, infectious diseases, Disorders of the central nervous system and other chronic diseases. This review covers the fundamental concepts associated with pharmaceutical nano-co-crystals, such as crystal engineering strategies, co-former selection, preparation methods, physicochemical characterization, and mechanisms of enhanced therapeutic efficacy. The latest developments in quality-by-design (QbD) techniques, continuous manufacturing, and computational crystal engineering and AI-assisted formulation design are critically reviewed as new tools to accelerate the development of nano-co-crystals. This review additionally emphasizes the combination of nano-co-crystals with advanced drug delivery technologies such as polymeric nanoparticles, liposomes, hydrogels and stimuli-responsive systems for precision therapies. There is also discussion of current regulatory issues, challenges in scaling up, intellectual property issues and barriers to clinical translation. Finally we discuss prospective directions for next generation hybrid crystal nanotechnology, multifunctional nano-co-crystal platforms and personalized healthcare. Nano-co-crystals close the gap between crystal engineering and state-of-the-art nanomedicine, enabling safer, more effective and targeted pharmaceutical treatments.

Keywords: Nano-co-crystals, Crystal engineering, precision drug delivery, Nanotechnology, Bioavailability enhancement

How to cite this article: Kohale NB, Tekade MS, Jawalkar GM, Jumble AS, Bodkhe AP, Bansod UR, Sawarkar HS. Nano-Co-crystals: Engineering Precision Drug Delivery through Hybrid Crystal Nanotechnology. Int J Drug Deliv Technol. 2026;16(76s): 1248-1257. DOI: 10.25258/ijddt.16.76s.112

1. Introduction

The clinical motivation for specific drug delivery mechanisms is to deliver therapeutic agents directly to diseased tissue without compromising healthy biological environments.[1-2] Traditional pharmacological treatments often suffer from low solubility, fast systemic clearance and non-specific biodistribution, leading to less effective therapeutic outcomes and serious side effects.[3] Nanotechnology has become a revolutionary approach that enables manipulation of materials at nanometer level to significantly improve the physicochemical properties and targeting abilities of pharmaceutical drugs.[4] Nano-cocrystals are a particularly interesting class of hybrid nanomaterials.[5] Such structures, based on the nanoscale combination of an active pharmaceutical ingredient with a stoichiometrically appropriate co-former, provide excellent flexibility in terms of dissolution rate, structural stability and payload capacity.[6] However, the reliable delivery of these nanococrystals to their desired biological targets, as well as the release of their contents in an optimal

kinetic manner, remains a significant engineering challenge.[7]

Despite the rapid progress in nanomedicine, there are still shortcomings in current targeted drug delivery strategies for several important reasons.[8-9] First, traditional strategies for the preparation of many functional nanomaterials usually demand harsh chemicals and hazardous reaction conditions, which can pose a serious threat to the health of patients and the environment at large.[10] Second, conventional platforms, such as drug-eluting stents or static microcapsules, generally lack the dynamic ability to adjust drug dosages or release kinetics in response to the real-time evolving status of diseased tissue.[11] Further, the manipulation of the motion of nanoscale drug carriers in dense biological fluids presents a major obstacle as diffusion limitations tend to decrease the overall efficiency of the delivery system.[12]

1.1. Controlled Release Systems and Kinetic Limitations

Dendrimers, gold nanoparticles, and customized microcapsules are just a few of the nanostructures that have been investigated in the quest for regulated therapeutic release.[13] For example, problems like in-stent restenosis often affect the long-term effectiveness of medical interventions like coronary stents.[14] This has led to the development of nano-assembled microcapsules loaded with functional nanoparticles to avoid negative biological events.[15] The goal of these systems is to stabilize pharmaceutical substances and offer a consistent release over a long time.[16] Additionally, there is growing interest in bacterial nanocellulose (BNC) as a very efficient carrier system. The usefulness of polymer-coated BNC fleeces as diffusion barriers for regulated medication release has been demonstrated by physics-based models.[17] These platforms often rely on static release profiles that are unable to adjust to the changing needs of the target tissue, although showing significant advantages over bare-metal or purely systemic approaches.[18-19]

Furthermore, these delivery platforms have intrinsic physical limitations that restrict their efficacy when depending on certain ligand-receptor interactions for cellular targeting.[20] The degree of cooperative binding is kinetically limited, according to theoretical and in vitro research on nano-complexes, such as dendrimers conjugated with folic acid to target overexpressed cancer receptors.[21] It's interesting to note that research suggests that weakening rather than strengthening individual connections can boost selectivity to specific cell types. Our suggested nano-co-crystal strategy aims to actively utilize these kinetic constraints in contrast to these other investigations. [22] We sought to create customizable binding affinities that maximize the residency period at the target cell membrane while averting premature systemic breakdown by carefully manipulating the co-former matrix of the crystal. [23-25]

1.2. Molecular Communication and Nano networks

Recently, molecular communication (MC) has become a revolutionary paradigm for intra-body drug delivery network modeling and engineering. [26] This conceptual framework models the biological environment as a probabilistic communication channel, treats drug carriers as transmitters, and uses sick cells as receivers. Researchers have suggested improved MC systems using localization-enabled relay networks, in which nano-controllers broadcast signals to ascertain the spatial clustering of drug-loaded nanomachines in relation to infected tissues, in order to solve the unreliability of solely diffusive transport. [27-28] Adopting cooperative quorum sensing, a density-dependent bacterial mechanism is another creative strategy.[29] In this method, drug release is only triggered by synthetic bacterium-based nano-machines when a particular molecular concentration threshold is reached. The goal of these extremely complex systems is to separate the drug absorption rate from the carrier's erratic mobility. [30]

Although mobile molecular communication frameworks are excellent at anticipating the channel impulse response and reducing the total amount of released drugs needed to attain a desired absorption rate, their implementation with conventional amorphous drugs is infamously challenging because of chemical instability during transit. [31] Our work expands the MC paradigm by using very stable nano-co-crystals in place of traditional fluidic or amorphous drug payloads. This hybrid nanomaterials strong crystalline lattice prevents the signaling molecules from breaking down too soon in the time-varying biological channel. [32] Our method offers a significantly more robust physical payload for advanced intra-body nanonetworks by connecting cooperative communication algorithms with solid-state hybrid crystal nanotechnology. [33]

1.3. Physical Actuation and BioMEMS Engineering

Physical actuation of drug delivery devices is a unique and important area of related study that goes beyond biochemical targeting and probabilistic

communication. [34] The development of mechanically active delivery platforms has been made possible by additive manufacturing and bio-microelectromechanical systems (BioMEMS).[35] Recent developments include, for instance, 3D-printed tumbling microrobots that are stereolithographically constructed and equipped with permanent micro-magnets that can be activated by rotating magnetic fields in physiological contexts. Simultaneously, pulsatile drug delivery devices that can produce and steer small drug droplets with great volumetric precision have been designed using electrohydrodynamic (EHD) production techniques. [36-37] Clinicians or automated systems can physically guide the therapy to the exact anatomical site thanks to these physical mechanisms, which provide unmatched spatial control over the delivery device. [38]

These physical actuation techniques have significant drawbacks despite their exceptional spatial precision. [39] Deep-tissue targeting in ambulatory individuals may not always be possible with magnetic microrobots since they sometimes require complicated, large external magnetic field generators.8 In a similar vein, EHD systems require the application of large external voltages, which may raise issues with electrochemical safety or localized heating in vivo. [40] These approaches are incorporated into our suggested architecture as additional nano-co-crystal delivery methods rather than as stand-alone solutions. We can drastically shorten the required actuation time by incorporating nano-co-crystals into electro-hydro-dynamically produced droplets or magnetically operated polymeric micro robots. [41] Drug efficacy is maintained during the high-stress physical deployment stages by the intrinsic structural stability of the nano-co-crystals, combining enhanced material resilience with mechanical accuracy. [42]

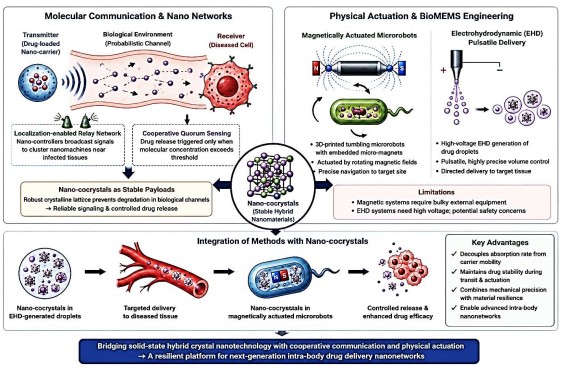

Figure1. Molecular Communication and BioMEMS Engineering

2. Method &Approach

2.1. Structured Framework for Nano-Co-crystal Delivery

Nano-co-crystal based drug delivery systems have received considerable attention as potential platforms for precision medicine due to their ability to improve drug solubility, targeted delivery and controlled therapeutic release. [43] Recent studies have shown multi-layered delivery designs that control the complete life cycle of nano-co-crystals, including their green production and targeted drug release. These combined systems combine advanced delivery methods with sustainable manufacturing practices to enhance treatment effectiveness and decrease systemic toxicity. [44]

Green nanotechnology has become a favored approach for creating hybrid nano-co-crystals since it removes the requirement for harmful chemicals and energy-demanding procedures. Bioreduction techniques that are plant-mediated and microbe-mediated employ naturally sourced phytochemicals and microbial byproducts as reducing and stabilizing agents, creating biocompatible nanostructures with limited environmental effects. In contrast to traditional physical and chemical synthesis techniques, these biological methods provide better sustainability, reduced toxicity, and greater compatibility with biological systems. [45] As a result, eco-friendly synthesized nano-co-crystals are being increasingly researched for pharmaceutical uses because of their advantageous safety characteristics and environmentally safe manufacturing. After synthesis, stabilizing nano-co-crystals is essential for preserving structural integrity throughout systemic circulation. [46-47]Various encapsulation strategies, including nano-assembled microcapsules, polymeric coatings, liposomes, hydrogels, and biodegradable nanocarriers, have been investigated to protect nano-co-crystals from premature dissolution and degradation. [48] Similar diffusion-barrier concepts have also been reported in bacterial nanocellulose-based drug delivery systems, where encapsulation matrices regulate drug transport while preserving the stability of the encapsulated therapeutic agents. [49]

Advanced nano-co-crystal delivery technologies need regulated drug release and targeted transport. Modern approaches involve the combination of passive targeting with active navigation employing ligand-

functionalized carriers, magnetic guidance or stimuli-responsive materials for targeted accumulation at diseased tissues. [50] Furthermore, computational and mathematical models are increasingly employed to predict and optimize release kinetics. Mathematical frameworks based on nonlinear dynamic models, diffusion-controlled transport and control theory such as sliding-mode control concepts have been explored to mimic nanoscale drug delivery and control therapeutic release under pre-determined physiological conditions. Many of these computational methods are still theoretical, but they demonstrate the growing convergence of systems engineering, mathematical modeling and nanomedicine for the precise control of drug delivery. [51] Many of these computational methods are still theoretical, but show the increasing integration of systems engineering, mathematical modeling and nanomedicine to control drug delivery with precision. Recent progress suggests that combining green synthesis, protective encapsulation, targeted navigation and mathematically guided release techniques is a critical approach in the development of next generation nano-co-crystal delivery systems. [52] Further progress in pharmaceutical nanotechnology, computational modeling, and materials science is expected to improve the therapeutic efficacy, safety, and clinical applicability of nano-co-crystal-based precision medicine. [53]

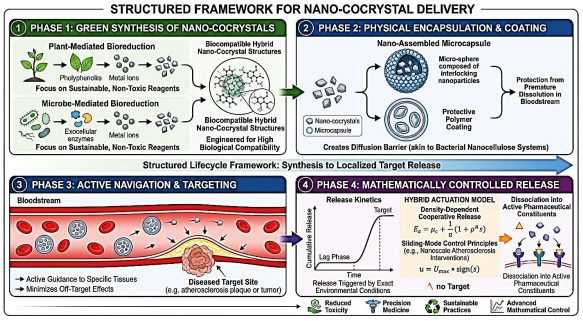

Figure2. Structured Framework for Nano-Co-crystal Delivery

3. General Workflow of Nano-Co-crystal-Based Drug Delivery Systems

Recent advances in nano-co-crystal drug delivery have resulted in integrated workflows with green synthesis, encapsulation, targeted navigation, and drug release control. Although each distribution platform has a different unique design, the literature identifies a generic implementation sequence. [54]

3.1. Green Synthesis and Nano-Co-crystal Formation

In the first step, eco-friendly methods are employed to synthesize the nano co-crystals. Green synthesis approaches employ plant extracts, microbial metabolites, or other biological reducing and stabilizing agents to self-assemble active medicinal ingredients with suitable co-formers into stable nano-co-crystal lattices. The methods get rid of the need for dangerous chemical reagents and improve biocompatibility, lower environmental impact and control particle size. [55]

3.2. Encapsulation and Carrier Integration

Nano-co-crystals are often added to protective carrier systems after manufacturing in order to increase stability in circulation and to increase the effectiveness of medication administration. Various encapsulation techniques have been studied, including polymeric nanoparticles, liposomes, hydrogels, nano-assembled microcapsules, electrohydrodynamically produced microdroplets, and stimuli-responsive carrier matrices. Recent studies have also investigated advanced delivery platforms, such as magnetically controlled microrobots and three-dimensional (3D)-printed microcarriers, to improve tissue penetration and site-specific delivery of drugs. [56]

3.3. Targeted Navigation and Molecular Communication

A key goal in precision medicine is to achieve targeted localization of nano-cocrystal carriers to diseased tissues. [57] Recently, molecular communication and nanonetwork-based approaches have been investigated, where carriers can estimate the proximity to target tissues via transmitting signals, relaying, and using localization algorithms. Such communication strategies seek to improve targeting accuracy, with low nonspecific distribution and systemic exposure. [58]

3.4. Stimuli-Responsive and Cooperative Drug Release

Stimulus-responsive drug release is generally triggered by specific physiological or pathological signals, such as pH, enzyme concentration, temperature, redox potential, or biomolecular signals in the target microenvironment. Motivated by naturally-occurring quorum sensing mechanisms,

several conceptual and computational studies have proposed cooperative release strategies, where therapeutic activation is only triggered once certain environmental or carrier-density thresholds are exceeded. The approaches aim to improve the specificity of drug release and to reduce premature drug leakage and off-target effects. [59-60]

Overall, the literature suggests that modern nano-co-crystal delivery systems adopt a modular design philosophy, allowing different carrier platforms, targeting mechanisms, and release strategies to be combined according to therapeutic requirements. This flexibility enables the integration of conventional nanocarriers, bacterial nanocellulose-based systems, microrobotic platforms, and mathematically controlled release models within a unified precision medicine framework. By maintaining the stability of nano-co-crystals during circulation and activating drug release only under appropriate biological conditions, these integrated delivery strategies have the potential to improve therapeutic efficacy while minimizing systemic toxicity.[60]

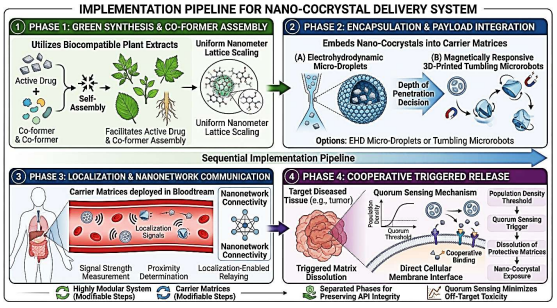

Figure3. Structured Framework for Nano-Co-crystal Delivery

4. Hypothetical Evaluation Plan

In order to prove the effectiveness of the proposed nano-co-crystal framework, we have developed a detailed but hypothetical evaluation plan. We present an in vivo simulation that benchmarks our hybrid system against conventional drug eluting platforms and freely diffusing amorphous nanoparticles. The hypothetical dataset will mimic an atherosclerotic arterial wall environment, to test the system's ability to navigate the high shear fluid dynamics and penetrate the endothelial layers. We will monitor the cumulative channel impulse response to evaluate the performance of the nano-co-crystals in overcoming the time-variant absorption rates due to the mobility of carriers. Performance metrics include target accumulation percentage, time to therapeutic concentration and exact reduction in collateral molecular distribution. [59]

In addition, a quantitative assessment of the kinetic binding limitations will be carried out. We will vary, in silico, the strength of ligand-receptor binding on the surface of the nano-co-crystals to empirically confirm the theoretical claim that weaker individual bonds may lead to improved cell specificity via co-operativity. The detailed pharmacodynamics readouts across the various bond strengths to be obtained in the evaluation plan will clearly demonstrate if the theoretically optimized nano-co-crystals will indeed outperform traditional delivery methods. We plan to show the clinical significance of the hybrid crystal methodology by quantifying the reduction of total drug consumption levels required to obtain therapeutic efficacy via rigorous nonlinear control simulation. [60]

5. Discussion

5.1. Practical Implications

The integration of nano-co-crystals in advanced targeted drug delivery systems has far-reaching practical implications for the future of personalized medicine. Highly engineered hybrid crystals can allow pharmaceutical developers to extend the shelf-life and in-vivo stability of sensitive therapeutics, moving away from standard amorphous drug formulations. This is especially important in the treatment of chronic diseases such as coronary artery disease, where the long-term efficacy of current drug-eluting stents is often compromised by adverse physiological responses. A dynamic system of robust nano-co-crystals could modulate the localized drug dose according to the exact diseased condition of the involved vessel, directly abating the spectrum of events resulting in late stent thrombosis or restenosis. Consequently, patients would require fewer invasive surgical interventions over their lifetimes, vastly improving overall clinical outcomes. [61]

Moreover, the application of mathematical models to define controlled release kinetics translates theoretical robustness into practical medical protocols. The ability to minimize the total amount of released drugs while strictly guaranteeing a desired rate of drug absorption allows the use of highly potent, highly toxic chemotherapeutic agents which would otherwise be unsafe for systemic administration. This points to a future clinical setting where oncologists and nanotechnologists collaborate to program specific physical and mathematical parameters into a patient's treatment regimen. The

result is a paradigm shift whereby the drug is not simply a passive chemical agent, but an active, communicative part of a larger biomechanical system.[62-63]

5.2. Limitations and Failure Modes

Despite the strong theoretical foundation of this proposed methodology, several technical limitations and potential failure modes must be explicitly addressed.

5.2.1. First, the degree of cooperative binding needed for high target specificity is constrained by local kinetic constraints. If the surface receptors on the biological target are expressed irregularly or dynamically, the mathematically optimized nano-co-crystals may not be retained on the cell membrane for a sufficient time, which leads to premature clearance.
5.2.2. Secondly, the use of molecular communication and nano networks makes them vulnerable to the deterioration of signals. The intra-body molecular channel has a high probability of obstruction and a complex turbulent flow dynamic, which can easily disturb the localization signals. In this case, the quorum sensing mechanism might not be activated and the therapeutic payload will be excreted without releasing the active drug.
5.2.3. Third, physical actuation approaches such as stereo lithography printed micro-robots or EHD droplet generation are limited by stringent operational constraints. High-voltage EHD systems and rotating magnetic field actuators demand complex external hardware that limits patient mobility. In addition, the geometric constraints of applying such external forces deep within complex tissue architectures can be prohibitive, limiting the application of actuated nano-co-crystals to superficial or highly accessible vascular environments. [64]

5.3. Ethical Considerations and Risks

There are serious ethical problems in moving hybrid crystal nanotech from theory to human trials. The biggest risk is the long-term toxicity that could come from the accumulation of degraded nanomaterials. Even with green synthesis methods with phytochemicals the long term biological footprint of artificially concentrated nano-co-crystals and their subsequent carrier matrix in human organs (liver and spleen) is still largely uncharacterized. There is an ethical obligation to demonstrate unequivocally that these nanoscale materials can be completely metabolized or safely eliminated without triggering chronic autoimmune reactions. Therapeutic availability and medical equity is another major ethical problem. The design, fabrication and mathematical control of nano co-crystal nanonetworks is highly complex. The first treatments will be too expensive to manufacture. Such precise drug delivery systems are at high risk of being available only in elite health-care settings, further widening existing gaps in global health outcomes. Researchers and policy-makers need to plan manufacturing and distribution strategies proactively to ensure that nanotechnology does not worsen the gap in patient survival rates as a function of socioeconomic status. [65-66]

6. Conclusion

In this paper we have laid down a comprehensive theoretical and methodological foundation for the use of nano-co-crystals as the central payload of sophisticated, precision pharmaceutical delivery systems. This combines the merits of the hybrid crystal stability with the environmental advantages of the green nanotechnology, thus giving rise to very biocompatible pharmaceutical agents. We have outlined how these sophisticated structures can be improved by incorporating mobile molecular communication principles, quorum sensing inspired release triggers and a rigorous mathematical sliding-mode control. This multi-disciplinary convergence can efficiently address the challenges of traditional therapeutic administration, such as diffusion limitations and poor kinetic adaptability. An interesting approach to overcome some important practical problems of complex biofluidic flow, such as signal blocking and kinetic binding limitations, is the formation of hybrid nanomaterials of solid state nanostructures and matrices for active deployment. The suggested combination of physical actuation mechanisms such as EHD generation and magnetic micro-robotics further ensures that future therapeutics can be actively directed to their targets with unprecedented spatial precision. Finally, the engineering of nano-co-crystals in such advanced technological settings has the potential to revolutionize targeted medical treatments, maximized the therapeutic efficacy and minimized the collateral systemic toxicity. These advances are further facilitated by green nanotechnology approaches that enable the synthesis of eco-friendly and biocompatible nanomaterials for targeted drug delivery applications.

Conflict of Interest
None

Acknowledgement

The authors express their sincere gratitude to the Management, Principal, and faculty members of Dr. Rajendra Gode College of Pharmacy, Amravati, for their continuous encouragement, valuable support, and for providing the necessary academic environment and facilities that enabled the successful completion of this review manuscript.

References

1. Karimi-Jafari, M.; Padrela, L.; Walker, G.M.; Croker, D.M. Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications. *Cryst. Growth Des.* **2018**, *18*, 6370–6387.
2. Bashimam, M.; El-Zein, H. Pharmaceutical cocrystal of antibiotic drugs: A comprehensive review. *Heliyon* **2022**, *8*, e11872.
3. Guo, M.; Sun, X.; Chen, J.; Cai, T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharm. Sin. B* **2021**, *11*, 2537–2564.
4. Li, Q.; Xie, Y.; Wang, Z.; Li, S.; Yang, S.; Yang, D.; Zhang, L.; Du, G.; Lu, Y. Optimization of physicochemical properties of theophylline by forming cocrystals with amino acids. *RSC Adv.* **2024**, *14*, 40006–40017.
5. Nikam, V.J.; Patil, S.B. Pharmaceutical cocrystals of nebivolol hydrochloride with enhanced solubility. *J. Cryst. Growth* **2020**, *534*, 125488.
6. Teng, R.; Wang, L.; Chen, M.; Fang, W.; Gao, Z.; Chai, Y.; Zhao, P.; Bao, Y. Amino acid based pharmaceutical cocrystals and hydrate cocrystals of the chlorothiazide: Structural studies and physicochemical properties. *J. Mol. Struct.* **2020**, *1217*, 128432.
7. Zhu, B.; Xia, M.; Ding, Z.; Rong, X.; Mei, X. Enhancing physical and chemical stability of hygroscopic hydroxytyrosol by cocrystal formation. *Int. J. Pharm.* **2023**, *646*, 123470.
8. Luo, Z.-K.; Qin, H.-M.; Han, J.-M.; Zhu, J.; Zeng, Y.-Y.; Fan, C.-P.; Liu, S.-X.; Hao, C.; Zhang, J.; Zhuang, T. Novel drug-drug co-amorphous systems of olaparib with nonsteroidal anti-inflammatory drugs with improved solubility, physical stability, antitumor activity and pharmacokinetics. *J. Drug Deliv. Sci. Technol.* **2024**, *101*, 106232.
9. Shaikh, R.; Singh, R.; Walker, G.M.; Croker, D.M. Pharmaceutical cocrystal drug products: An outlook on product development. *Trends Pharmacol. Sci.* **2018**, *39*, 1033–1048.
10. Wong, S.N.; Chen, Y.C.S.; Xuan, B.; Sun, C.C.; Chow, S.F. Cocrystal engineering of pharmaceutical solids: Therapeutic potential and challenges. *CrystEngComm* **2021**, *23*, 7005–7038.
11. Bolla, G.; Sarma, B.; Nangia, A.K. Crystal engineering of pharmaceutical cocrystals in the discovery and development of improved drugs. *Chem. Rev.* **2022**, *122*, 11514–11603.
12. Kumar, A.; Nanda, A. In-silico methods of cocrystal screening: A review on tools for rational design of pharmaceutical cocrystals. *J. Drug Deliv. Sci. Technol.* **2021**, *63*, 102527.
13. Sakhiya, D.C.; Borkhataria, C.H. A review on advancement of cocrystallization approach and a brief on screening, formulation and characterization of the same. *Heliyon* **2024**, *10*, e29057.
14. Parkes, A.; Ziaee, A.; O'Reilly, E. Evaluating experimental, knowledge-based and computational cocrystal screening methods to advance drug-drug cocrystal fixed-dose combination development. *Eur. J. Pharm. Sci.* **2024**, *203*, 106931
15. Guidetti, M.; Hilfiker, R.; Kuentz, M.; Bauer-Brandl, A.; Blatter, F. Exploring the cocrystal landscape of Posaconazole by combining high-throughput screening experimentation with computational chemistry. *Cryst. Growth Des.* **2023**, *23*, 842–852.
16. Singh, M.; Barua, H.; Jyothi, V.G.S.S.; Dhondale, M.R.; Nambiar, A.G.; Agrawal, A.K.; Kumar, P.; Shastri, N.R.; Kumar, D. Cocrystals by Design: A Rational Coformer Selection Approach for Tackling the API Problems. *Pharmaceutics* **2023**, *15*, 1161.
17. Molajafari, F.; Li, T.; Abbasichaleshtori, M.; Moein Hajian, D.Z.; Cozzolino, A.F.; Fandrick, D.R.; Howe, J.D. Computational screening for prediction of co-crystals: Method comparison and experimental validation. *CrystEngComm* **2024**, *26*, 1620–1636.
18. Solares-Briones, M.; Coyote-Dotor, G.; Páez-Franco, J.C.; Zermeño-Ortega, M.R.; De la o Contreras, C.M.; Canseco-González, D.; Avila-Sorrosa, A.; Morales-Morales, D.; Germán-Acacio, J.M. Mechanochemistry: A Green Approach in the Preparation of Pharmaceutical Cocrystals. *Pharmaceutics* **2021**, *13*, 790.
19. Aitipamula, S.; Bolla, G. Optimizing Drug Development: Harnessing the Sustainability of Pharmaceutical Cocrystals. *Mol. Pharm.* **2024**, *21*, 3121–3143
20. Chettri, A.; Subba, A.; Singh, G.P.; Bag, P.P. Pharmaceutical co-crystals: A green way to enhance drug stability and solubility for improved therapeutic efficacy. *J. Pharm. Pharmacol.* **2024**, *76*, 1–12.
21. Baldea, I.; Moldovan, R.; Nagy, A.-L.; Filip, G.A.; David, L.; Olteanu, D.E.; Ionescu, C.M.; Filip, C.; Dehelean, C.A. Ketoconazole–fumaric acid pharmaceutical cocrystal: From formulation design for bioavailability improvement to biocompatibility

testing and antifungal efficacy evaluation. *Int. J. Mol. Sci.* **2024**, *25*, 13346.
22. Paulazzi, A.R.; Alves, B.O.; Zilli, G.A.; Diniz, A.; Mussi, S.V.; Almeida, L.; Pergher, S.B.C.; Nunes, R.J.; de Araujo, M.B. Curcumin–N-acetylcysteine cocrystal produced with supercritical solvent: Characterization, solubility, and preclinical evaluation of antinociceptive and anti-inflammatory activities. *Inflammopharmacology* **2022**, *30*, 1671–1685.
23. Wong, S.N.; Low, K.-H.; Poon, Y.L.; Zhang, X.; Chan, H.W.; Chow, S.F. Synthesis of the first remdesivir cocrystal: Design, characterization, and therapeutic potential for pulmonary delivery. *Int. J. Pharm.* **2023**, *640*, 122983.
24. Wong, S.N.; Li, S.; Low, K.-H.; Chan, H.W.; Zhang, X.; Chow, S.; Hui, B.; Chow, P.C.Y.; Chow, S.F. Development of favipiravir dry powders for intranasal delivery: An integrated cocrystal and particle engineering approach via spray freeze drying. *Int. J. Pharm.* **2024**, *653*, 123896.
25. Machado, T.C.; Gelain, A.B.; Rosa, J.; Cardoso, S.G.; Caon, T. Cocrystallization as a novel approach to enhance the transdermal administration of meloxicam. *Eur. J. Pharm. Sci.* **2018**, *123*, 184–190
26. Samie, A.; Alavian, H.; Vafaei-Pour, Z.; Mohammadpour, A.H.; Jafarian, A.H.; Danesh, N.M.; Abnous, K.; Taghdisi, S.M. Accelerated Wound Healing with a Diminutive Scar through Cocrystal Engineered Curcumin. *Mol. Pharm.* **2023**, *20*, 5090–5107.
27. Qiao, N.; Wang, K.; Schlindwein, W.; Davies, A.; Li, M. In situ monitoring of carbamazepine–nicotinamide cocrystal intrinsic dissolution behaviour. *Eur. J. Pharm. Biopharm.* **2013**, *83*, 415–426.
28. Alhalaweh, A.; Roy, L.; Rodríguez-Hornedo, N.; Velaga, S.P. pH-dependent solubility of indomethacin–saccharin and carbamazepine–saccharin cocrystals in aqueous media. *Mol. Pharm.* **2012**, *9*, 2605–2612.
29. Bhardwaj, S.; Lipert, M.P.; Bak, A. Mitigating cocrystal physical-stability liabilities in preclinical formulations. *J. Pharm. Sci.* **2017**, *106*, 31–38.
30. Yamashita, H.; Sun, C.C. Improving Dissolution Rate of Carbamazepine-Glutaric Acid Cocrystal Through Solubilization by Excess Coformer. *Pharm. Res.* **2018**, *35*, 4.
31. Omori, M.; Sugano, K. Solution-Mediated Phase Transformation on Crystal Facets of Carbamazepine–Saccharin Cocrystals. *Cryst. Growth Des.* **2021**, *21*, 6237–6244. Tatsumi, Y.; Shimoyama, Y.; Kazarian, S.G. Analysis of the Dissolution Behavior of Theophylline and Its Cocrystal Using ATR-FTIR Spectroscopic Imaging. *Mol. Pharm.* **2024**, *21*, 3233–3239.
32. Jia, Y.; Yang, D.; Wang, W.; Hu, K.; Yan, M.; Zhang, L.; Gao, L.; Lu, Y. Recent advances in pharmaceutical cocrystals of theophylline. *Nat. Prod. Bioprospect.* **2024**, *14*, 53.
33. Tong, Y.; Wang, Z.; Yang, E.; Pan, B.; Dang, L.; Wei, H. Insights into cocrystal polymorphic transformation mechanism of ethenzamide-saccharin: A combined experimental and simulative study. *Cryst. Growth Des.* **2016**, *16*, 5118–5126.
34. Xuan, B.; Chen, Y.C.S.; Wong, K.C.; Chen, R.; Lo, P.S.; Lakerveld, R.; Tong, H.H.Y.; Chow, S.F. Impacto f cocrystal solution-state stability on cocrystal dissociation and polymorphic Drug recrystallization during dissolution. *Int. J. Pharm.* **2021**, *610*, 121239.
35. Kimoto, K.; Yamamoto, M.; Karashima, M.; Hohokabe, M.; Takeda, J.; Yamamoto, K.; Ikeda, Y. Pharmaceutical cocrystal development of TAK-020 with enhanced oral absorption. *Crystals* **2020**, *10*, 211.
36. Shi, K.; Li, M. Optimisation of pharmaceutical cocrystal dissolution performance through a synergistic precipitation inhibition. *Pharm. Res.* **2023**, *40*, 2051–2069.
37. Guo, C.; Zhang, Q.; Zhu, B.; Zhang, Z.; Bao, J.; Ding, Q.; Ren, G.; Mei, X. Pharmaceutical Cocrystals of Nicorandil with Enhanced Chemical Stability and Sustained Release. *Cryst. Growth Des.* **2020**, *20*, 6995–7005.
38. Alvani, A.; Shayanfar, A. Solution Stability of Pharmaceutical Cocrystals. *Cryst. Growth Des.* **2022**, *22*, 6323–6337Xuan, B.; Wong, S.N.; Zhang, Y.; Weng, J.; Tong, H.H.Y.; Wang, C.; Sun, C.C.; Chow, S.F. Extended reléase of highly wáter soluble isoniazid attained through cocrystallization with curcumin. *Cryst. Growth Des.* **2020**, *20*, 1951–1960.
39. ClinicalTrials.gov. Efficacy and Safety of LCZ696 Compared to Enalapril in Patients with Heart Failure (PARADIGM-HF), NCT01035255. Available online: **https://clinicaltrials.gov/study/NCT01035255** (accessed on 14 January 2025).
40. Khder, Y.; Shi, V.; McMurray, J.J.V.; Lefkowitz, M.P. Sacubitril/Valsartan (LCZ696) in Heart Failure. *Handb. Exp. Pharmacol.* **2017**, *243*, 133–165.
41. Novartis, A.G. Solid-State Forms of Sacubitril and Valsartan (LCZ696). U.S. Patent US20090203754A1, 13 August 2009.
42. Videla, S.; Lahjou, M.; Vaqué, A.; Sust, M.; Encabo, M.; Soler, L.; Sans, A.; Sicard, E.; Gascón, N.; Encina, G.; et al. Single-dose pharmacokinetics of co-crystal of tramadol–celecoxib: Results of a four-way randomized open-label phase I clinical trial in healthy subjects. *Br. J. Clin. Pharmacol.* **2017**, *83*, 2718–2728

43. Cebrecos, J.; Carlson, J.D.; Encina, G.; Lahjou, M.; Sans, A.; Sust, M.; Vaqué, A.; Morte, A.; Gascón, N.; Plata-Salamán, C. Celecoxib-tramadol co-crystal: A Randomized 4-Way Crossover Comparative Bioavailability Study. *Clin. Ther.* **2021**, *43*, 1051–1065.
44. Langford, R.; Morte, A.; Sust, M.; Cebrecos, J.; Vaqué, A.; Ortiz, E.; Fettiplace, J.; Adeyemi, S.; Raba, G.; But-Husaim, L.; et al. Efficacy and safety of co-crystal of tramadol-celecoxib (CTC) in acute moderate-to-severe pain after abdominal hysterectomy: A randomized, double-blind, phase 3 trial (STARDOM2). *Eur. J. Pain.* **2022**, *26*, 2083–2096.
45. Langford, R.; Viscusi, E.R.; Morte, A.; Cebrecos, J.; Sust, M.; Giménez-Arnau, J.M.; De Leon-Casasola, O. Efficacy of Co-Crystal of Tramadol-Celecoxib (CTC) in Patients with Acute Moderate-to-Severe Pain: A Pooled Analysis of Data from Two Phase 3 Randomized Clinical Trials. *Drugs RD* **2024**, *24*, 239–252.
46. Fediuk, D.J.; Nucci, G.; Dawra, V.K.; Cutler, D.L.; Amin, N.B.; Terra, S.G.; Boyd, R.A.; Krishna, R.; Sahasrabudhe, V. Overview of the Clinical Pharmacology of Ertugliflozin, a Novel Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor. *Clin. Pharmacokinet.* **2020**, *59*, 949–965.
47. Wong, S.N.; Weng, J.; Ip, I.; Chen, R.; Lakerveld, R.; Telford, R.; Blagden, N.; Scowen, I.J.; Chow, S.F. Rational Development of a Carrier-Free Dry Powder Inhalation Formulation for Respiratory Viral Infections via Quality by Design: A Drug-Drug Cocrystal of Favipiravir and Theophylline. *Pharmaceutics* **2022**, *14*, 300.
48. Alipour, S.; Mahmoudi, L.; Ahmadi, F. Pulmonary drug delivery: An effective and convenient delivery route to combat COVID-19. *Drug Deliv. Transl. Res.* **2022**, *13*, 705–715.
49. Boboltz, A.; Kumar, S.; Duncan, G.A. Inhaled drug delivery for the targeted treatment of asthma. *Adv. Drug Deliv. Rev.* **2023**, *198*, 114858.
50. Karashima, M.; Sano, N.; Yamamoto, S.; Arai, Y.; Yamamoto, K.; Amano, N.; Ikeda, Y. Enhanced pulmonary absorption of poorly soluble itraconazole by micronized cocrystal dry powder formulations. *Eur. J. Pharm. Biopharm.* **2017**, *115*, 65–72.
51. Al-Obaidi, H.; Granger, A.; Hibbard, T.; Opesanwo, S. Pulmonary Drug Delivery of Antimicrobials and Anticancer Drugs Using Solid Dispersions. *Pharmaceutics* **2021**, *13*, 1056.
52. Tanaka, R.; Hattori, Y.; Otsuka, M.; Ashizawa, K. Application of spray freeze drying to theophylline-oxalic acid cocrystal engineering for inhaled dry powder technology. *Drug Dev. Ind. Pharm.* **2020**, *46*, 179–187.
53. Sun, X.; Castro-Dominguez, B. Electrosprayed co-crystals of levofloxacin for inhalation: A strategy for excipient-free dry powder antibiotics. *Int. J. Pharm.* **2025**, *688*, 126454.
54. Yu, Y.-M.; Yu, M.-C.; Wang, L.-Y.; Li, Y.-T.; Wu, Z.-Y.; Yan, C.-W. 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 J. Chem.* **2020**, *44*, 15994–16005.
55. Ray, E.; Vaghasiya, K.; Sharma, A.; Shukla, R.; Khan, R.; Kumar, A.; Verma, R.K. Autophagy-Inducing Inhalable Co-crystal Formulation of Niclosamide-Nicotinamide for Lung Cancer Therapy. *AAPS PharmSciTech* **2020**, *21*, 260.
56. Safarov, R.; Fedotova, O.; Uvarova, A.; Gordienko, M.; Menshutina, N. Review of Intranasal Active Pharmaceutical Ingredient Delivery Systems. *Pharmaceuticals* **2024**, *17*, 1180.
57. Ghadiri, M.; Young, P.M.; Traini, D. Strategies to Enhance Drug Absorption via Nasal and Pulmonary Routes. *Pharmaceutics* **2019**, *11*, 113.
58. Rai, G.; Gauba, P.; Dang, S. Recent advances in nanotechnology for Intra-nasal drug delivery and clinical applications. *J. Drug Deliv. Sci. Technol.* **2023**, *86*, 104726
59. Decuzzi P, Ferrari M. The receptor-mediated endocytosis of nonspherical particles. Biophysical Journal. 2008;94(10):3790–3797.https://doi.org/10.1529/biophysj.107.12283
60. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annual Review of Biomedical Engineering. 2012;14:1–16. https://doi.org/10.1146/annurev-bioeng-071811-150124
61. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. Nature Reviews Materials. 2016;1:16014. https://doi.org/10.1038/natrevmats.2016.14
62. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Advanced Drug Delivery Reviews. 2014;66:2–25. https://doi.org/10.1016/j.addr.2013.11.009
63. Karagianni A, Malamatari M, Kachrimanis K. Pharmaceutical cocrystals: New solid phase modification approaches for the formulation of APIs. Pharmaceutics. 2018;10(1):18.
64. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical cocrystals: Along the path to improved medicines. Chemical Communications. 2016;52:640–655.
65. Kipp JE. The role of solid nanoparticle technology in pharmaceutical development. International Journal of Pharmaceutics. 2004;284:109–122.

66. Thipparaboina R, Kumar D, Chavan RB, Shastri NR. Multidrug co-crystals: Towards the development of effective therapeutic hybrids. Drug Discovery Today. 2016;21:481–490.