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Review Paper

Microwave-Assisted Synthesis: A Green Chemistry Approach for Drug Cocrystals Synthesis

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Abstract
Microwave-assisted synthesis (MAS) presents a promising approach to the formation of pharmaceutical cocrystals, offering notable improvements in solubility, dissolution rate, stability, and bioavailability of active pharmaceutical ingredients (APIs). This review aims to evaluate the potential of MAS as a green and efficient strategy for drug cocrystal synthesis, particularly in comparison to conventional methods such as solvent evaporation, slurry crystallisation, and grinding techniques. A systematic literature review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, to ensure a comprehensive selection of relevant studies. The analysis focused on reported synthesis methods, cocrystal formation under microwave exposure, reaction conditions, yields, purity, and scalability outcomes of MAS compared to conventional techniques. This review also highlight current applications, critical synthesis parameters, and challenges such as penetration depth, reaction uniformity, and thermal control. Findings indicate that MAS significantly reduces reaction time, minimizes solvent use, and enhances product purity and yield. Its compatibility with solvent-free or minimal-solvent processes aligns closely with green chemistry principles, making it a sustainable alternative. Furthermore, MAS effectively addresses solubility mismatches and process inefficiencies commonly encountered in traditional methods. The future prospect of MAS lies in its integration with continuous manufacturing, automation, and drug repurposing efforts, which could revolutionize pharmaceutical formulation by accelerating innovation while adhering to environmental and regulatory standards.

Keywords
Microwave-Assisted Synthesis, Green Chemistry, Drug Cocrystal Synthesis

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1. INTRODUCTION

The discovery of new chemical entities (NCEs) often encounters significant physicochemical challenges, such as poor solubility, low permeability, and limited bioavailability (Hodgson, 2001). In fact, nearly 90% of drug candidates in development exhibit poor solubility (Loftsson and Brewster, 2010). As a result, reformulating existing medicines has become a more viable and profitable strategy than developing new ones. The pharmaceutical industry, facing a shortage of innovative molecules that can successfully reach the market (Drews and Ryser, 1996), has increasingly turned to enhancing existing drugs through better formulations. These reformulations offer opportunities to improve efficacy and marketability, especially for drugs already known to suffer from poor solubility (Kalepu and Nekkanti, 2015).

Various techniques have been developed to address these solubility issues. Salt formation is among the most established methods (Serajuddin, 2007; Joshi and Roy Choudhury, 2018), while others include the use of nanoparticles (Zeng et al., 2021), cosolvency (Miyako et al., 2010), and solid dispersions (Wegiel et al., 2014). However, salt formation is only applicable to ionisable compounds, and other methods may suffer from thermodynamic instability. An emerging alternative is the formation of cocrystal, which offer the advantage of increased solubility without requiring ionisable functional groups (Liu et al., 2022). Additionally, cocrystals tend to exhibit greater thermodynamic

stability and better mechanical properties, making them well-suited for tablet formulation (Yadav et al., 2009; Taylor and Day, 2018).

Pharmaceutical cocrystals are defined as multicomponent crystalline materials composed of an active pharmaceutical ingredient (API) and one or more coformers, held together by noncovalent interactions within the same crystal lattice (Desiraju, 1995). According to the FDA, cocrystals are "crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredients and cocrystal formers, in the same crystal lattice" (Food and Drug Administration, U.S. Department of Health and Human Services, 2018). These components are present in defined stoichiometric ratios and interact through hydrogen bonding, π-π stacking, or van der Waals forces (Aitipamula et al., 2012; Alvani and Shayanfar, 2022). Cocrystals are widely studied in both academia and industry for their potential to enhance solubility (Zhou et al., 2016; Kang et al., 2017), bioavailability (McNamara et al., 2006; Smith et al., 2011), stability (Trask et al., 2006; Huang and Rodríguez-Hornedo, 2011), hygroscopicity (Wang et al., 2011), and compressibility (Ouyang et al., 2024).

Among various methods for producing cocrystals, solution crystallisation is frequently used (Liu et al., 2022). However, this method is unsuitable when the solubilities of the API and coformer differ significantly and typically requires large volumes of solvent, which may result in environmental contamination (Friščić and Jones, 2010; Friščić, 2012; Pagire et al., 2013). Other strategies, such as neat and liquid-assisted grinding, are more environmentally friendly (Karki et al., 2007) but may yield cocrystals with low purity and poor crystallinity. Liquid-assisted grinding is also hindered by its dependence on solvent type, stoichiometric variability, and limited scalability (Trask and Jones, 2005). Solvent-free methods like twin-screw extrusion and melt crystallisation show promise, yet carry risks of thermal degradation and high mechanical stress (Medina et al., 2010; Kelly et al., 2012; Pagire et al., 2013; Yan et al., 2015).

Given these limitations, there is a growing need for greener, more efficient synthesis techniques. Green chemistry offers a sustainable path forward by minimising hazardous substances, energy use, and waste throughout the drug development cycle (Martinengo et al., 2024; Ahmad et al., 2024). Conventional cocrystal synthesis methods often fall short of these principles due to high solvent use, long reaction times, and scalability issues (Kappe, 2004; Pagire et al., 2013). Adopting green chemistry approaches can enhance both environmental safety and manufacturing efficiency.

A promising solution is microwave-assisted synthesis (MAS), a technique aligned with green chemistry principles that has been successfully applied in organic synthesis (de la Hoz et al., 2016; Kumar et al., 2020; Xochicale-Santana et al., 2021; Li et al., 2024). Although MAS is well-known in organic chemistry, its application to cocrystal synthesis is still emerging. Microwave irradiation offers rapid, uniform heating, which drastically reduces reaction time and often eliminates the need for organic solvents (Gawande et al., 2014; Kou et al., 2023; Ahmad et al., 2024). This method enhances process efficiency and minimises environmental impact (de la Hoz et al., 2016; Xochicale-Santana et al., 2021; Anastas and Warner, 2023; Ahmad et al., 2024).

While green approaches have been explored in cocrystal synthesis, there remains a significant gap in the application of microwave-assisted synthesis (MAS) for this purpose. Most published studies focus on conventional synthesis methods or explore MAS only in general chemical contexts, without specific emphasis on its use in drug cocrystal formation. This underexplored area represents an opportunity to advance both the scientific understanding and practical application of MAS in pharmaceutical formulation.

This review aims to address the research gap by systematically exploring the potential of microwave-assisted synthesis in pharmaceutical cocrystal formation. It focuses on understanding the underlying heating mechanisms, evaluating key process parameters, and assessing the method's suitability for industrial-scale application. In addition, this review presents current research findings on MAS in pharmaceutical applications and provides practical guidance for laboratory setup and troubleshooting during synthesis.

To answer the main research questions-how cocrystals form under microwave irradiation and what critical parameters must be controlled during synthesis-a systematic literature review was conducted following PRISMA guidelines (Page et al., 2021). Articles were retrieved from Scopus and Google Scholar using the keywords "microwave" and "cocrystals." The review included studies published between 2010 and 2025 that reported the synthesis and characterisation of drug cocrystals using MAS, either alone or in combination with other methods. Review articles and studies not directly related to drug cocrystal synthesis were excluded. Due to the limited number of publications specifically focused on MAS in cocrystal synthesis, references from broader chemical synthesis literature were also included to provide foundational understanding and contextual relevance.

2. PRINCIPLES OF MICROWAVE HEATING

Microwave irradiation is electromagnetic irradiation, in which the region lies between infrared and radio frequencies (Figure 1). Microwave reactors for synthesis operate at a frequency of 2.45 GHz. In the microwave irradiation area, an electric field will arise. Therefore the microwave-assisted synthesis (MAS) principle is based on the dielectric heating principle. This heating only occurs when materials are polar, i.e. molecules with a permanent or induced dipole moment that respon to the electric field (Kappe and Stadler, 2005).

Dielectric heating in an electric field resulting from microwave irradiation occurs via dipolar polarisation and ionic conduction (Lidström et al., 2001; Kappe and Stadler, 2005). Dielectric heating transforms electric energy into kinetic energy, leading to heat generation. In the dipolar polarisation mechanism (Figure 2a), the material must be polar, i.e., the

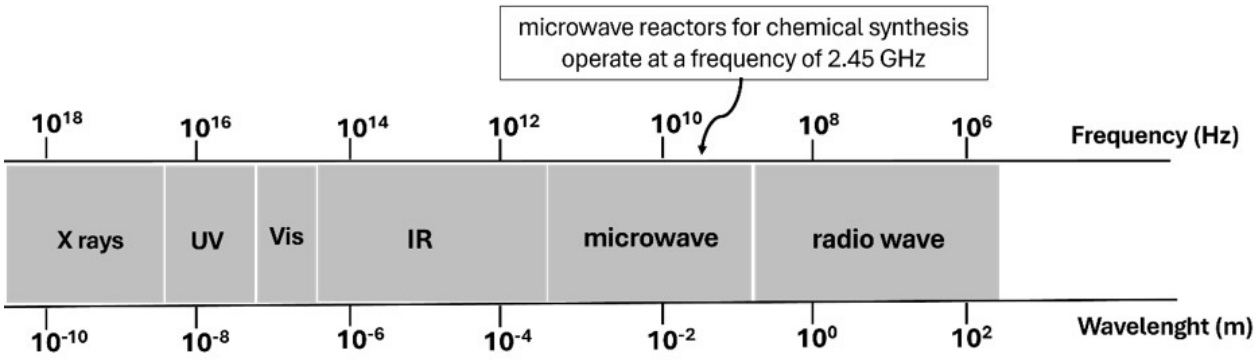

Figure 1. Electromagnetic Spectrum: Microwave Irradiation is Electromagnetic Irradiation in the Frequency Range 0.3 Ghz To 300 Ghz

molecule structure is partly negatively and positively charged-only these materials can absorb microwave energy. Microwave irradiation generates an electric field that oscillates. The polar molecule absorbs energy when its electric field dipoles align with the oscillating field. This molecular dipole alignment creates friction at the molecular level, which is converted into heat as long as microwave exposure, i.e. electric field exposure. The ability of the molecule to align itself with the frequency of the applied field will determine the amount of heat generated (Lidström et al., 2001; Kappe and Stadler, 2005). While in the ionic conduction (Figure 2b) heating mechanism, the requirement for this induction is that the molecule must be completely dissolved and ionised. The ionic molecule oscillates back and forth under microwave irradiation, i.e. electric field. This oscillation causes frequent collisions of the charged particles with neighbouring molecules, creating heat energy (Kappe and Stadler, 2005).

Whether dipolar polarisation or ionic conduction, microwa ve irradiation simultaneously raises the temperature of the whole reaction mixture volume. This heating process is called bulk heating (Adepu and Ramakrishna, 2021). Microwave irradiation interacts selectively and directly with the "core" of the material. While in conventional heating, heat is transferred from the surface of the vessel or material mixture to the core through conduction (Sabelström et al., 2014; Dandia et al., 2021). This is why microwave irradiation produces uniform and efficient heating throughout the sample (Wäppling Raaholt and Isaksson, 2017; Jeon et al., 2022; Tangjaideborisut et al., 2025) compared to conventional heating. This mechanism significantly reduces reaction times and enhances reaction rates (Bogdal, 2005; Gawande et al., 2014).

The heating efficiency in microwave-assisted synthesis (MA S) is determined by the dielectric properties of the material, including the dielectric constant (ε'), dielectric loss (ε''), and polarity. ε'' (dielectric loss) represents the efficiency of the material in absorbing and converting electromagnetic radiation into heat. ε' is the dielectric constant describing the polarizability of the molecules in the electric field. At a particular frequency and temperature under microwave irradiation, the capability of a substance in generating heat is expressed as the loss factor tan $\delta=\varepsilon/\varepsilon$ (Kappe, 2004; Kappe and Stadler, 2005; Kappe et al., 2013).

Based on the above explanation, microwave irradiation generates heat differently with different solvents, reagents, and catalysts in the reaction mixture, depending on each dielectric property. Thus, it is rational that the process can be modified by combining other materials to the reaction mixture to enhance the heating efficiency, i.e. heat rate and intensity. Commonly used materials to alter the process besides the catalysts in the reaction mixture include organic solvents. They are typically classified based on the dielectric loss (tan δ) into high (tan δ >0.5), medium (tan δ = 0.1-0.5), and low microwave absorbing (tan δ <0.1). The higher the tan δ value of a substance, the more rapid its heating under microwave irradiation (Bao et al., 2023). It explains that it is still possible for non-polar materials to be synthesised using MAS as long as polar solvents are included to absorb microwave energy, leading to heat generation.

The selectivity of microwave interaction with materials that can only absorb its energy results in heating efficiency during synthesis. The interaction makes the heating process fast and efficient because it does not go through the process of initiating surface induction on the vessel but directly on the core of the material (molecule level heating) (Figure 3a). Initial surface heating on the material or vessel surface is a process in which conventional heating is applied (Figure 3b). This process is usually lengthy because the heat does not generate directly but has to travel deeper into the reaction mixture. In contrast, microwave irradiation heats the mixture on a molecular level by direct interaction with molecules and avoids the initial heating of the vessel surface. By microwave irradiation, the temperature inside the reaction mixture rises throughout the volume simultaneously (bulk heating) (Meloni et al., 2023; Horikoshi et al., 2024). The rapid heat distribution prevents the formation of hot spots, ensuring a homogeneous temperature distribution and uniform heating throughout the material.

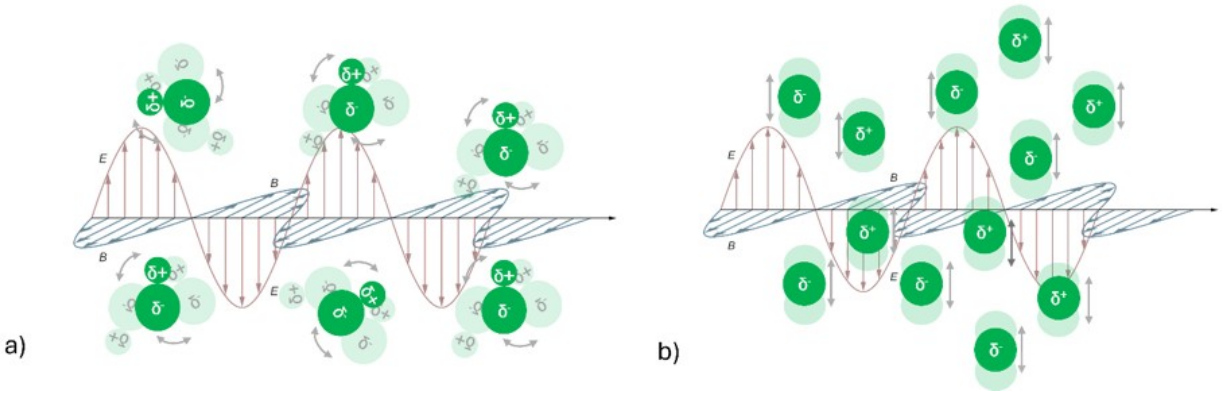

Figure 2. Illustration of Dielectric Heating Dipole Alignment in Oscillating Electric Field (E), a) Dipolar Polarisation, b) Ionic Conduction

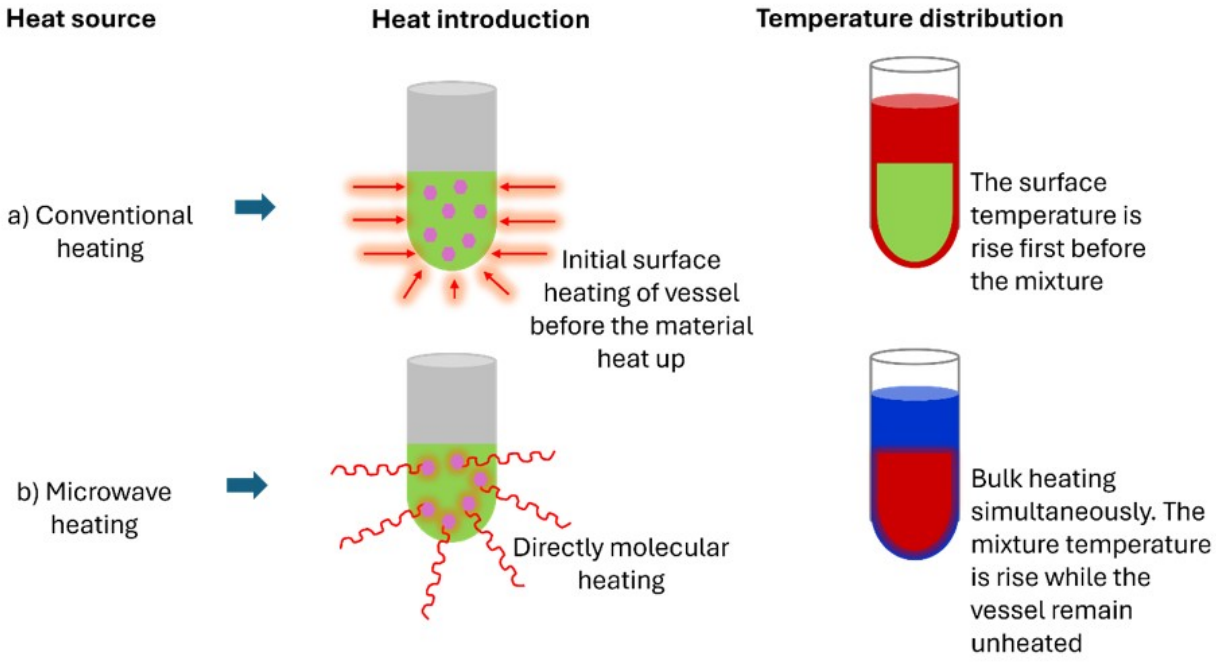

Figure 3. Heat Introduction and Temperature Distribution Into and Inside A Reaction Mixture for (a) Conventional Heating and (b) Microwave Heating

3. FEASIBILITY OF USING MICROWAVE-ASSISTED COCRYSTAL SYNTHESIS FOR COCRYSTALS

The feasibility of using microwave-assisted synthesis (MAS) for cocrystal formation is strongly influenced by the material properties of the active pharmaceutical ingredient (API), co-former, and any solvents used—particularly their dielectric and thermal characteristics. One of the key advantages of MAS lies in its ability to selectively and rapidly heat materials based on their dielectric properties. Polar compounds exhibit high dielectric constants (ε') and loss tangent values ($\tan\delta$), making them highly responsive to microwave irradiation and thus feasible to be synthesized using MAS. This inherent responsiveness significantly improves reaction rates and energy efficiency (Kappe and Stadler, 2005; Kumar et al., 2020).

For non-polar compounds, MAS remains feasible through the use of polar solvents or additives, which can enhance the overall dielectric properties of the reaction mixture. Because solvent dielectric constants and tan δ values are well-document ed, they are often used as practical indicators to estimate the heating efficiency of the entire reaction system. In most cocrystal systems, either the API or the coformer is polar, making it highly likely that the reaction mixture will be suitable for microwave heating. A list of solvents with commonly reported tan δ values is presented in Table 1 (Bao et al., 2023), serving as a useful reference for selecting suitable conditions.

Since microwave heating is driven by the dielectric constant,

Table 1. Common Organic Solvents and Their Tan δ

Solvent	ε'	ε"	tan δ	Microwave Adsorption Capacity
Ethanol	24.3	22.86	0.941	high
Dimethyl sulfoxide	48.9	40.34	0.825	high
Formic acid	58.5	42.24	0.722	high
Methanol	32.6	21.48	0.659	high
Ethanoic acid	6.19	1.08	0.174	medium
Dichloroethane	10.4	1.32	0.127	medium
Water	80.4	9.89	0.123	medium
Ethyl acetate	6.03	0.356	0.059	low
Acetone	20.7	1.11	0.054	low
Hexane	1.9	0.038	0.020	low

Note: ε' Is the dielectric constant, ε'' is the dielectric loss, and tan δ is the tangent of loss or loss factor. The microwave absorption capacity is categorised into "high" for tan $\delta > 0.5$, "medium" for $0.1 <$ tan $\delta < 0.5$, and "low" for tan $\delta < 0.1$. Source: (Bao et al., 2023)

dielectric loss, and polarity of the material, its effectiveness correlates directly with polarity during the reaction process (Mishra et al., 2015). All those variables are influenced by the solvent's functional groups, and together they determine its microwave absorption capacity. Polarity arises from the presence of polar functional groups, such as hydroxyl (−OH), carboxylic acid (−COOH), or sulfoxide (S=O), which create molecular dipoles. These polar groups generally increase the dielectric constant (ε'), measure of the material's ability to store electrical energy in an electric field. However, efficient microwave heating also depends on the solvent's ability to dissipate that energy as heat, represented by the dielectric loss (ε''). The ratio of ε'' to ε', known as the loss tangent (tan δ), ultimately defines how well a solvent absorbs microwave energy. For example, solvents with highly polar functional groups and high ε'' values, such as ethanol, formic acid, and dimethyl sulfoxide, exhibit high microwave absorption capacity (high tan δ) (see Table 1). From Table 1, it can be concluded that we cannot say that the more polar a material is, the higher its absorption capacity will be. We must consider the dielectric loss of a material, given that microwave absorption capacity is calculated based on the ratio of dielectric loss to dielectric constant.

In addition to dielectric behavior, thermal stability of the materials is crucial. All reactants and the resulting cocrystal must withstand the temperatures reached during microwave exposure. If thermal degradation occurs, MAS may not be appropriate for that system. Nevertheless, for a wide range of pharmaceutical compounds with adequate thermal tolerance and dielectric responsiveness, MAS offers a highly feasible, efficient, and environmentally friendly synthesis route for cocrystal formation.

4. MECHANISMS OF COCRYSTAL FORMATION VIA MAS

The fundamental principle of forming a cocrystal depends on the molecules recognising one another to make intermolecular interactions, forming a supramolecular synthon (Friščić, 2012), leading to nucleation and finally crystallisation (Desiraju, 2013). In cocrystal, the interaction is particularly through hydrogen bonding, π-π stacking, and van der Waals interactions that drive the formation of cocrystals (Desiraju, 2010; Pindelska et al., 2017; Saha et al., 2023). The molecules must move, meet, and align to build a crystal nucleus and grow. In this context, molecules need energy to move from the crystal lattice of each reactant, i.e. API and coformer, and ensure that intermolecular interactions occur to form a new crystal lattice. It should be emphasised that there is no bond breaking in the molecular structure in this process, and the intermolecular interactions are noncovalent. This limitation is in line with the definition of cocrystal (Desiraju, 1995; Aitipamula et al., 2012; Bolla et al., 2022).

Thus, the primary goal of obtaining energy from microwave irradiation is not to induce covalent bond formation or breaking but to facilitate molecules' mobility and noncovalent interaction. When molecules in the reaction mixture can interact with an electric field, i.e. dielectric heating mechanism, the heat will accumulate and increase the kinetic energy of the material and enables chemical reactions (Bogdal, 2005). The kinetic energy leads to molecular mobility enhancement and intermolecular collisions' frequency. This mechanism is advantageous in cocrystal synthesis, where molecules must move and interact with other molecules (Huang et al., 2021). Consequently, the probability of hydrogen bond formation between functional groups is improved. Intermolecular interactions form immediately once molecules find energetically favourable orientations (Musumeci et al., 2011). This indicates that for the purpose of cocrystal formation, the control lies in the setting of the energy level, i.e. the level of heating produced by microwave irradiation. If the microwave power is too high or the exposure is too long, the energy can lead to the degradation of hydrogen-bonded assemblies or even decomposition. This isothermal holds at strategic temperatures is employed, especially near the melting point of the components. This provides sufficient molecular mobility for alignment into the desired supramolecular synthon formation without crossing into decomposition or chemical reaction regimes.

The primary difference between MAS and conventional methods in cocrystal formation lies in the speed and efficiency of the process. In contrast, the fundamental principle in cocrystal nucleation remains the same (molecule mobility, alignment, and supramolecular synthon formation) (Desiraju, 2013; Bavishi and Borkhataria, 2016). Direct molecules heating through dielectric heating, causing rapid heating at the molecular level. This leads to quicker molecular motion, higher collision frequency, leading to more efficient hydrogen bonding or noncovalent interactions. Meanwhile, conventional methods such as solvent evaporation, slurry mixing, or grinding rely on slower

heat transfer via conduction or convection. This means reactions typically require longer times to reach the necessary temperatures, and heat may not be uniformly distributed, leading to less efficient formation of cocrystals and possibly uneven crystallisation.

How exactly do the cocrystals start to form a nucleus and grow after microwave heating. Cocrystals form when two (or more) different molecules, an API and a conformer, self-assemble driven by noncovalent interactions like hydrogen bonding, π–π stacking, or van der Waals forces (Friščić, 2012). For this to happen, the molecules must move and meet, and that is where diffusion comes in. Microwaves at 2.45 GHz can enhance diffusion. Transport of an active species is a rate-limiting step in a reaction, and microwaves enhance the diffusion of that species. The diffusion enhancement leads to an enhanced reaction rate compared to conventional heating (Antonio and Deam, 2007). The alternating electromagnetic field appears to promote the solid phase transformation beyond the effect of just the temperature increase (Ahuja et al., 2020). Increased molecular mobility and complementarity will initiate the cocrystal formation (Jayasankar et al., 2006; Chadwick et al., 2007; Guo et al., 2010). Below are the ordered steps of cocrystal formation (Figure 4):

1. *Microwave irradiation*. Delivers dielectric heating, activating polar molecules.
2. *Molecular mobility*. It means molecular diffusion. Molecules must move to come into contact and establish intermolecular interactions. This can occur in solution (bulk diffusion), solid–liquid interface (surface diffusion), or solid–solid contact surfaces (limited but possible at elevated energy levels, e.g., microwave, grinding). With the presence of microwave irradiation, the electric field will interact with polar molecules, i.e., API, coformer, solvent, causing dielectric heating. This molecular interaction leads to rapid and uniform heating throughout the reaction mixture. This heating increases molecular motion, promoting the diffusion of API and coformer molecules. This enhanced mobility allows the molecules to come into proximity, promoting interactions necessary for cocrystal formation. Diffusion must always involve building molecular aggregation because molecules must meet, align, and interact. No matter the method, molecules must move from one place to another to find each other, form noncovalent interactions, and build a crystal lattice. This is why the diffusion rate directly affects nucleation speed, which depends on heat generation. It can be stated that microwave irradiation helps push the "pedal" of the molecules to move. At the same time, the diffusion is the engine that drives molecules to find each other and align properly based on the supramolecular synthon principle to build a cocrystal.
3. *Molecular orientation*. When molecules are mobile, it means they begin to diffuse. The orientation of API molecules and conformer is directional since the molecules meet the requirement of supramolecular synthon theory (Desiraju, 1995, 2010, 2013).
4. *Nucleation*. Once API and conformer molecules align properly and build noncovalent interactions repeatedly, they form a nucleus — the seed of a cocrystal (Desiraju, 2010; Bavishi and Borkhataria, 2016). Through noncovalent interactions such as hydrogen bonding, π–π stacking, or van der Waals forces, the API and coformer organise into a new crystalline lattice, forming the desired cocrystal. Continued diffusion brings more molecules to the nucleus, allowing it to grow into a visible crystal.
5. *Crystal growth*. Diffusion continues to supply new molecules to the crystal front. The crystal will grow as long as the system remains supersaturated (in solution) or activated by energy input (in the solid state).

Crystallisation of cocrystal is about getting molecules to meet, align properly, and interact noncovalently. For that to be possible, molecular diffusion - the movement of molecules through a solvent or between solid particles - is key. It indicates that even if there is no solvent as a medium, it is still possible to form a cocrystal by surface contact between the materials in the reaction mixture. In MAS, diffusion is enhanced by localised heating in which microwaves heat selectively, i.e. polar materials absorb energy quickly. Even a small amount of polar solvent can help enhance the heat efficiency, leading to the mobilisation of molecules at the particle surfaces immediately. This creates localised "hot spots" and increases molecular motion, accelerating interface diffusion.

In addition to assisting in heating, using solvent in MAS will serve as a medium and enhance diffusion. Even a small amount of solvent can help mobilise molecules at the particle surfaces. This is the basis of solvent-drop grinding or liquid-assisted grinding. The reactants do not need to dissolve entirely in the solvent during crystallisation. A study by Ahuja et al. (2020) demonstrates that microwave-assisted slurry conversion crystallisation significantly accelerates cocrystal formation compared to conventional heating methods (Guo et al., 2018; Ahuja et al., 2020). Even in solid-state systems like neat grinding, the conventional method of cocrystal synthesis, there is still surface diffusion (limited molecular contact zones). Hence, increased kinetic energy of molecules by microwave irradiation will accelerate diffusion on both molecular and interfacial scales and increase the speed of forming cocrystals even in the solid state of the reaction mixture. Without diffusion, molecules would stay locked in their original positions, and no cocrystal would form. So, regardless of method, diffusion is the fundamental molecular engine. What changes are speed, energy source (microwave, mechanical, thermal), and medium (liquid, surface, vapour, solid). In combination with rapid and efficient heating, a high-pressure environment in closed microwave systems, pressure builds up. This can increase solvent penetration and accelerate diffusion into the particle.

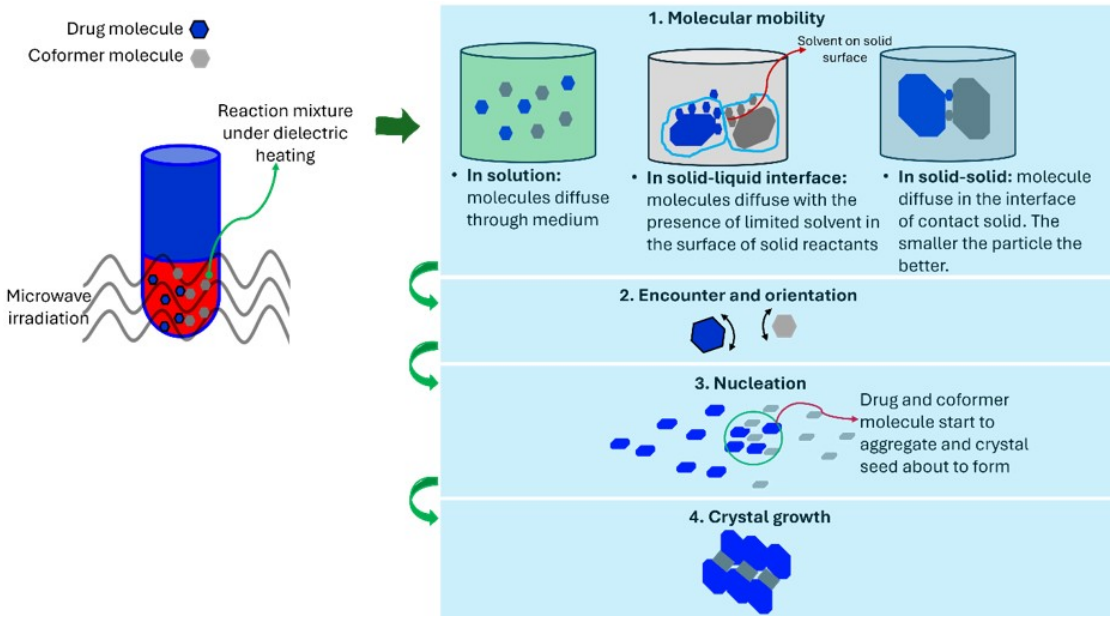

Figure 4. Steps Oof Cocrystal Formation Under MAS

5. COMPARISON OF MAS WITH CONVENTIONAL METHODS

The most commonly used conventional methods for synthesising cocrystals include solvent evaporation, slurry crystallisation, neat grinding, and liquid-assisted grinding (Guo et al., 2021). In conventional methods of cocrystal formation, general principles of cocrystal formation remain applicable, i.e. diffusion is the primary initial driving force for intermolecular interactions and the formation of noncovalent cocrystal components (Kuroda et al., 2004; Friščić and Jones, 2009; Karimi-Jafari et al., 2018).

In the solvent evaporation method, the active pharmaceutical ingredient (API) and the coformer are dissolved in a suitable solvent. When the solvent evaporates, supersaturation of the solution components is achieved. This supersaturation leads to closer contact between the molecules, making it more likely for intermolecular interactions to be established. The solvent evaporation rate and concentration gradient are critical in controlling cocrystal nucleation and growth (Weyna et al., 2009; Modani et al., 2020).

In the slurry crystallisation method, a solid API is suspended in a solvent containing the coformer. Over time, diffusion allows the coformer molecules to move toward the API particles, forming cocrystals at the solid-liquid interface. In this method, each component gradually dissolves and forms a complex to promote the nucleation and growth of cocrystals. The efficiency of this process depends on factors such as temperature, solvent choice, and the stirring rate, which influence the diffusion rates of the coformer molecules (Huang et al., 2019; Pantwalawalkar et al., 2025).

Meanwhile, neat grinding methods involve the API and coformer being physically mixed in grinding techniques. This method sometimes needs a small amount of solvent (liquid-assisted grinding). The mechanical energy applied during grinding increases the surface area and promotes molecular diffusion between the components, leading to cocrystal formation. In grinding methods, molecular diffusion happens in the solid state, where components are brought into close contact mechanically. This method facilitates molecular diffusion at a microscopic level as the components grind against each other. While this does not rely on diffusion through a solvent, the mechanical force enables the molecules to interact and form cocrystals. Though diffusion is still a factor, conventional grinding may not reach the localised heating or pressure that microwaves can provide, leading to slower formation of the cocrystals than MAS (Hossain Mithu et al., 2021; Rong et al., 2023; Pantwalawalkar et al., 2025).

In essence, diffusion occurs both in conventional and MAS, but in conventional methods, it tends to be slower due to less uniform heating and longer reaction times. The advantages of MAS compared to the conventional method of cocrystal synthesis is that the heating mechanism provides a rapid and efficient process. MAS accelerates molecular diffusion by delivering rapid and uniform heating, making molecular interactions and cocrystal formation faster and more efficient. This increases molecular mobility, allowing molecules to diffuse more effectively and interact quickly to form hydrogen bonds. When solvent is involved, the localised heating in MAS often creates higher supersaturation and more rapid nucleation, which speeds up the entire process, including diffusion.

Energy efficiency was reported to be multiple times better for microwave-heated processes than conventionally heated processes (Priecel and Lopez-Sanchez, 2019). This is one of the main advantage of MAS. Microwaves enable direct and

selective heating of reactants, minimising wasted energy and lowering overall consumption. This allows significantly faster synthesis, leading to much shorter reaction times than conventional grinding or solvent-based methods (Pagire et al., 2013). A good yield and purity of cocrystal obtained using microwave-assisted synthesis are another benefit of using this method (Sahoo and Banik, 2020; Martina et al., 2021; Ioniţă et al., 2024).

Compared to the conventional method, however, solvent dependency, stoichiometric diversity and lack of scalability are important issues in the liquid-assisted grinding technique, which limit its applicability. Another well-explored technique for cocrystal synthesis is neat or liquid-assisted grinding (Trask et al., 2006). It is an environmentally friendly approach limited by the lack of purity of the resulting cocrystal and the formation of disordered crystals with reduced particle size (Trask and Jones, 2005). Conventionally, cocrystals are produced by solution crystallisation. However, this is unsuitable when there is a significant difference in the solubility of the two components (Guo et al., 2010; Friščić, 2012).

Despite its advantages, MAS also faces several limitations. The effect of penetration depth must also be considered in microwave reactions. Penetration depth refers to the depth at which the microwave intensity decreases from its original intensity (Zhang and Hayward, 2006). It should be noted that if the penetration depth is much smaller than the size of the material, only the surface of the incident wave will absorb the energy, leading to non-uniform heating (Li et al., 2025). MAS also presents optimisation challenges, as the precise control of reaction uniformity and reproducibility can be difficult to achieve, especially in heterogeneous mixtures where microwave absorption varies between components (Priecel and Lopez-Sanchez, 2019). An additional drawback is the risk of thermal degradation, where the localised and rapid heating intrinsic to microwave irradiation can lead to overheating and decomposition of thermally sensitive active pharmaceutical ingredients (APIs) and coformers (Kappe, 2004; Kappe and Stadler, 2005). Table 2 below summarises the comparison between the MAS cocrystal synthesis method and the conventional method.

6. CRITICAL PARAMETER PROCESS ON MICROWAVE-ASSISTED COCRYSTAL SYNTHESIS

6.1 Microwave Power (Wattage)

Microwave power refers to the amount of energy the microwave delivers to the reaction system, typically measured in watts (W), i.e. the temperature setting. Understanding and controlling this parameter is essential because it directly influences how fast and how much the sample heats up (Kappe and Stadler, 2005). Maintaining an optimal energy level during chemical processes ensures efficient reaction progress without surpassing the reactants' or products' thermal stability limits. Overheating may occur if the energy input is too high, causing the breaking of chemical bonds and resulting in undesirable side reactions or complete decomposition of the target compound. In a standard commercially available microwave for chemical synthesis, the temperature is set at a desired target temperature, and the system automatically adjusts the power to maintain it. In the next section, this paper will discuss a technical approach and troubleshooting in setting up the microwave power (Kappe, 2004).

6.2 Temperature Target

The desired temperature target must be achieved and maintained during synthesis, where the reaction is expected to be completed. The temperature target should balance reaction speed while preventing thermal decomposition. Control of target temperature is critical for optimal nucleation and crystal growth without damaging the reactant. For a cocrystal formation, setting the temperature below the melting points of the individual components will be sufficient while preventing material decomposition (Pagire et al., 2013; Lin et al., 2014; Ketkar et al., 2016; Ioniţă et al., 2024). If the heat is above or above the melting points, it is more likely to cause thermal degradation.

6.3 Reaction Time

Reaction time refers to the period during which the reactants are exposed to microwave irradiation at the desired set conditions (usually a controlled temperature and pressure). This reaction time is also termed the hold time. Since irradiation time will determine the heat generated on the reaction mixture (Wang et al., 2011), insufficient hold time may lead to an incomplete reaction. In contrast, excessive time could lead to decomposition or undesired phases.

6.4 Pressure

The MAS system is usually in a closed vessel. When microwaves heat the reaction mixture, the temperature can rise rapidly, causing the solvent and reactants to vaporise and generate pressure. This elevated pressure allows the reaction mixture to remain in the liquid phase at temperatures above its normal boiling point, often accelerating reaction rates.

Commercially available microwave reactors became controllable by temperature monitoring and pressure sensing, and therefore safe and reproducible. The combination of sealed vessels and rapid microwave heating opens up new possibilities in chemistry, allowing reactions to be performed quickly and efficiently under elevated temperature and pressure conditions (Kappe, 2004).

6.5 Stirring

Stirring promotes uniform heat and mass transfer throughout the reaction mixture. Microwaves tend to heat materials unevenly, especially in heterogeneous systems where differences in dielectric properties can cause localised hotspots (Horikoshi et al., 2013; Mohd Fuad et al., 2019; Li et al., 2025). Stirring helps to distribute heat evenly, preventing temperature gradients that might lead to side reactions or incomplete conversion of reactants. Stirring can also increase inter-molecular or inter-particle collisions, thus improving reaction kinetics. In

Table 2. Comparison Between MAS and Conventional Cocrystal Synthesis Methods

Method	Heating Type	Solvent Use	Reaction Time	Purity/Yield	Energy Efficiency
Microwave-Assisted Synthesis	Rapid, volumetric (dielectric)	Optional	Minutes	High	High
Solvent Evaporation	External heating	High	Hours to days	Moderate to high	Low to moderate
Slurry Crystallisation	External heating	Moderate	Hours to days	Moderate	Low
Neat Grinding	Mechanical energy	None	Minutes to hours	Variable	Moderate
Liquid-Assisted Grinding	Mechanical	Minimal	Minutes to hours	Moderate	Moderate

solid-liquid or multiphase systems, stirring prevents sedimentation and maintains consistent contact between the reactants (Kappe, 2004; Kappe and Stadler, 2005).

6.6 Microwave Exposure Mode (Continuous vs. Pulsed)

Microwave exposure mode refers to how microwave energy is delivered to a reaction system during Microwave-Assisted Synthesis (MAS). The two main modes are continuous and pulsed. In continuous mode, microwave energy is supplied steadily at a constant power level throughout the reaction time. This provides consistent heating, which is ideal for reactions requiring stable and uniform temperatures. Continuous mode helps maintain a steady reaction rate and often leads to faster completion, especially for processes that benefit from sustained high temperatures. In pulsed mode, microwave energy is delivered in intervals; the power switches on and off in cycles. This mode helps control excessive heat and pressure buildup, especially in sensitive reactions or when working with volatile solvents. Pulsed exposure allows the reaction mixture to cool slightly between microwave bursts, preventing overheating, reducing decomposition risks, and allowing for better control over reaction kinetics (Kappe, 2004; Herrero et al., 2008; Kappe et al., 2013).

7. ECO-FRIENDLY ASPECTS OF MICROWAVE-ASSISTED COCRYSTAL SYNTHESIS

Microwave-assisted cocrystal synthesis is an environmentally friendly approach that aligns with the 12 Principles of Green Chemistry (Anastas and Warner, 2023). Microwave irradiation promotes rapid and energy-efficient heating, significantly reducing reaction times and minimising energy consumption. This aligns with Principle number 6 of 12 Principles of Green Chemistry, i.e. Design for Energy Efficiency. Microwave-assisted processes also enable solvent-free or minimal-solvent conditions (Principle 5: Safer Solvents and Auxiliaries), decreasing the reliance on hazardous organic solvents and reducing waste generation (Principle 1: Prevention). The enhanced reaction control achievable through microwave irradiation also supports safer operational conditions (Principle 12: Inherently Safer Chemistry for Accident Prevention) by minimising the risk of thermal runaway and pressure build-up (Kappe, 2004). Furthermore, the precision of microwave heating can improve product selectivity and yield, which contributes to minimising by-products and resource waste (Principle 2: Atom Economy and Principle 9: Catalysis when applicable). These aspects demonstrate that microwave-assisted cocrystal synthesis is an effective strategy for pharmaceutical and material science applications and a sustainable methodology that embodies the core values of green chemistry (Loupy, 2004; Martinengo et al., 2024).

8. CURRENT APPLICATIONS OF MAS IN COCRYSTAL SYNTHESIS

In the range of 2010-2025, the author has searched for research publications related to the use of MAS for drug cocrystal synthesis (Table 3). The scope of the search is limited to research results that apply MAS singly or combined with other conventional methods for drug cocrystal synthesis.

9. FUTURE PERSPECTIVES

9.1 Perspective on Development and Scale-Up

The future perspective on the industrial adoption of MAS is promising, particularly as advancements in reactor design and process control continue to address existing limitations (Ku et al., 2002; Priecel and Lopez-Sanchez, 2019; Martina et al., 2021; Li et al., 2025). A key focus for future development is the creation of large-scale, automated microwave reactors capable of delivering uniform energy distribution across substantial reaction volumes, which would resolve one of the main challenges associated with scaling up laboratory-scale protocols. Overcoming equipment limitations, such as microwave penetration depth and temperature measurement accuracy, will make MAS a viable alternative for large-batch chemical production (Kappe and Stadler, 2005; Wäppling Raaholt and Isaksson, 2017; Kalinke et al., 2022). Optimising critical process parameters, including temperature control, power, operating pressure, stirring efficiency, and microwave exposure mode, will ensure reproducibility, product consistency, and drug safety at an industrial scale (Anandam and Selvamuthukumar, 2014; Makgabutlane et al., 2020; Albuquerque et al., 2021; An et al., 2025). The technique shows strong scalability

Table 3. Key Features of Cocrystallisation Involving MAS

API-coformer	Procedure	Heating Profile	Observation	Ref.
Caffeine–Maleic acid	Solvent-free and solvent (water, methanol, acetone, toluene, ethyl acetate) mediated cocrystallisation experiments	Using a microwave reactor Monowave 300, Anton Paar Gmbh, Austria, with a target temperature set at 80°C, a hold time of 60s was used.	The overall process depends on the solubility of solvent components and the solutions' dielectric properties <the researchers do not report thermal analysis>	(Pagire et al., 2013)
Theophylline (THE) – Acetylsalicylic acid (ASA)	Slurry mixture in ethanol, then subject to microwave irradiation	Microwave irradiation at 600W for 6 min	The microwave-assisted irradiation of the grinded mixture accelerates the cocrystal formation between the two precursors. Cocrystal was not obtained by simply mixing ASA and THE in the absence of microwave irradiation, both in the presence and absence of absolute ethanol as solvent. Based on DSC measurement, the endothermic peak is 272.9°C for theophylline and 140.2°C for acetylsalicylic acid. The new cocrystal has an endothermic peak at 129.3°C.	(Fuliaş et al., 2014)
Indometacin Nicotinamide	Cocrystal was prepared using solvent evaporation and neat grinding, then subjected to microwave irradiation for evaporation.	A domestic microwave oven (TMO-202; Tatung Company, Taipei, Republic of China) with a power of 800W is used to heat and evaporate the sample to approximately 78°C after 3 min of irradiation.	Microwave heating quickly results in cocrystal formation compared to slow evaporation with or without stirring at ambient temperature, fast evaporation at 50°C, and solvent-assisted grinding (20 min in a ceramic mortar) after adding three drops of ethyl acetate. It is strongly suggested that cocrystal formation would be accelerated and assisted by the thermal effect of microwave irradiation via the rapid evaporation of ethyl acetate. Based on DSC measurement, the indometacin has an endothermic peak at 163°C and 131°C for nicotinamide, while the resulting cocrystal is 126°C.	(Lin et al., 2014)
Carbamazepine Succinic acid	Cogrinding slurry method (absolute ethanol) following the subjection of the physical mixture to microwave irradiation	Using the Elta domestic oven at 500W for 7 min	The cocrystal formation was easy and reproducible. Based on the DSC measurement, the carbamazepine has an endothermic peak at 187°C and succinic acid at 189°C, while the resulting cocrystal is 209°C.	(Fuliaş et al., 2015)
Caffeic acid phenethyl ester (CAPE) – caffeine (CAF), isonicotinamide (INIC), and nicotinamide (NIC)	Slurry mixture using ethanol, then subjected to microwave irradiation	Using microwave reactor Monowave 300, Anton Paar, Gmbh, Austria. The operating conditions were set at a target temperature of 80°C and a hold time of 60 s, followed by cooling to 40°C	The study confirms successful formation of novel cocrystals using microwave-assisted cocrystallisation of the para-methoxy cinnamic acid technique. CAPE has a melting point of 129°C, 129.4°C for NIC, 158.23°C for INIC, 236.73°C for CAF, while the resulting crystalline CAPE-NIC has a melting point of 107.01°C, CAPE-INIC has 106.35°C, and CAPE-CAF has 113.64°C.	(Ketkar et al., 2016)

Para-methoxy cinnamic acid (pMCA)	Manual mixing in water, then subjected to microwave irradiation	Using a domestic microwave oven at 450 Watts of radiation power (Sharp R-728 (W) -IN) set for 15 min.	Cocrystal sample synthesised using the microwave radiation method provides the highest solubility and dissolution because the microwave radiation during the synthesis process could induce better formation of cocrystals. The pMCA and caffeine have endothermic peaks at 173.56°C and 235.87°C, respectively. At the same time, the resulting cocrystal has enothermic peak around 150-125°C.	(Sulistyowaty et al., 2024a)
para methoxycin-nami acid (pMCA)-Succinic Acid	Manual mixing in methanol, then subjected to microwave irradiation	Domestic microwave at 540W for 20 min	Synthesis using microwave irradiation was faster (20 min) than solvent evaporation 48 hrs. The pMCA has an endothermic peak at 173.56°C and succinic acid at 189.31°C. The resulting cocrystal has an endothermic peak at 159.50°C	(Sulistyowaty et al., 2024b)
Resveratrol Piperazine	The reactant mixture was prepared in two ways prior to being subjected to microwave irradiation: Solubilisation in ethanolic solution; Slurry mixture	Using Miniflow 200SS microwave laboratory equipment: Sample in solution: the experiments were conducted at 30°C, 40°C, 50°C and 60°C under magnetic stirring of 50 rpm, 50W microwave irradiation power and a frequency of 2450 MHz, for 6 min. Also assessed at 40°C within 12 min of microwave irradiation; Sample in slurry: the experiments were performed using a temperature of 30°C, a power of 100W and 200 rpm magnetic stirring, for 5, 10 and 15 min.	Shorter synthesis time compared to conventional methods (2–15 min). Reproducible synthesis of the resveratrol-piperazine cocrystal. All the resulting cocrystal has endothermic peaks around 205.7–206.8°C, piperazine has an endothermic peak at around 100-125°C, and resveratrol at around 250-275°C	(Ioniţă et al., 2024)
Sulfamethazine Nicoti-namide, Sulfamer-azine Anthranilic acid, Sulfam-erazine Salicylamide	The slurry mixture was then subjected to microwave irradiation	Using microwave automatic reactor, ATPIO XO-SM100, 0–1000W. Temperature set at 70°C for 4 minutes under continuous stirring at 120 rpm	Microwaves, as the heating source, are found to increase the rate at which co-crystals are formed, compared to standard heating	(Ahuja et al., 2020)
Diclofenac acid - Proline	Liquid-assisted and neat grinding then subjected to microwave irradiation	Domestic microwave (MW) with low energy (399W) and observed in 1 minute	A stable and uniform diclofenac-proline co-crystal was efficiently generated	(Nugrahani et al., 2019)

Diclofenac acid - Proline	Top-down and bottom-up methods were used to produce nano-sized cocrystals. The top-down process was carried out by wet milling procedure and neat grinding procedures, while the bottom-up process used globule inversion phase and fast evaporation assisted microwaving-ach of the resulting mixtures was subjected to microwave irradiation.	Using a domestic microwave SHARP, R-230R(S), Tokyo, Japan , 776 W for about 10 min.	Nano-sized cocrystal of diclofenac acid-proline was successfully produced using the fast evaporation assisted by the microwave method.	(Nugrahani and Auli, 2020)

potential, particularly its compatibility with continuous-flow microwave reactors, making it an attractive option for laboratory research and industrial-scale production (Priecel and Lopez-Sanchez, 2019).

Continuous flow microwave reactors offer a scalable and efficient pathway for mass production, including in pharmaceutical manufacturing. Continuous flow is the performance of chemical reactions using a continuous stirred tank reactor rather than in a traditional batch stirred vessel. A large-scale continuous flow chemistry processing has been widely used in industrial chemical production (Harmsen, 2010; Baumann et al., 2020). This approach addresses the common limitations of batch microwave processing, such as poor scalability and uneven heating, while significantly reducing reaction times and energy consumption. Several companies have integrated continuous flow microwave reactors into their pharmaceutical development pipelines. For example, CEM Corporation has commercialised a microwave reactor which has been used for both small-scale and scale-up microwave-assisted organic synthesis (Ferguson, 2003; Goyal et al., 2020).

9.2 Research Opportunities

Future research on microwave-assisted synthesis (MAS) of drug cocrystals should aim to deepen understanding of the fundamental mechanisms that govern energy transfer and molecular interaction under microwave irradiation. This includes investigating how different microwave parameters-such as power input, frequency, and irradiation time-influence nucleation, crystal growth, and polymorphic outcomes across various drug coformer systems. Moreover, integrating MAS with real-time analytical techniques such as in situ spectroscopy or thermal imaging could enable better monitoring and control of cocrystal formation processes.

Additionally, integrating MAS with milling techniques such as ball milling (Fischer et al., 2016; Ioniţă et al., 2024), is an exciting research prospect, particularly for drug cocrystal synthesis. Both techniques have procedures that minimise the use of solvents, coupled with the advantages of efficient MAS in terms of synthesis time efficiency. Hence, combining the two is an interesting strategy for green chemistry. The potential synergism between these two approaches is that milling results in small particle sizes that allow for increased surface contact between particles. At the same time, microwave heating accelerates molecular interactions and energy transfer at the reaction site.

MAS offers significant research opportunities when integrated with Quality by Design (QbD) (Ross et al., 2024) principles and Process Analytical Technology (PAT) (Moradiya et al., 2016; Chavan et al., 2018), both of which aim to enhance process understanding, control, and product quality in pharmaceutical manufacturing. QbD emphasises designing processes that consistently yield products meeting predefined quality attributes, with MAS providing a robust platform for process optimisation. In conjunction with PAT, which involves real-time monitoring and control of critical process parameters, MAS can facilitate continuous feedback loops to optimise reaction conditions. For example, sensors integrated into microwave reactors can measure real-time temperature, pressure and concentration. Such a design allows data to be obtained that can be used for product quality control to obtain consistent results. Thus, applying MAS in pharmaceutical manufacturing aligns with good drug manufacturing practices' QbD and PAT requirements.

10. RESEARCH TECHNIQUES AND TROUBLESHOOT IN MAS

10.1 Getting Started with MAS for Cocrystal Synthesis

Since microwave-assisted synthesis was introduced, experiments were typically carried out in sealed vessels utilising domestic household microwave ovens without any chance for temperature or pressure measurement. The results were often uncontrolled heating, which led to degradation. The situation changed when microwave reactors were introduced in 2000 for scientific use. Microwave synthesis reactions have now become controllable by temperature monitoring and pressure sensing, and therefore safe and reproducible (Kappe, 2004; Kappe and Stadler, 2005).

Considering the importance of controlling critical process parameters in MAS, it is necessary to define the appropriate instrument settings, including target temperature, ramp temperature, holding time, and stirring speed. Many specialised microwave reactors are commercially available, which allows researchers to establish those parameters. Below are the ordered steps to getting started:

1. *Target temperature*. Target temperature is the specific reaction temperature the microwave system aims to reach and maintain during the synthesis. The instrument adjusts the microwave power automatically to reach and maintain that temperature. In this case, the delivery input energy is set based on the temperature needed to initiate the desired reaction. Determining the microwave temperature target for cocrystal synthesis depends on factors like solvent choice, the thermal stability of API, and the coformer. A high microwave absorption solvent, a polar solvent like ethanol and methanol, uses lower temperatures, i.e. lower power (300–400 W), to prevent excessive heating. Low microwave absorption, especially for solid-state reactants or non-polar solvents, uses higher temperatures, i.e. higher power (500–600 W), to ensure efficient heating (Bao et al., 2023). Estimating the right temperature for cocrystal formation in MAS is important; if it is too low and nothing happens, it is too high, and we risk decomposition or eutectic melting instead of cocrystallisation. To determine the optimal target temperature for MAS of cocrystals, the melting points of the active pharmaceutical ingredient and the coformer serve as essential reference points. Since cocrystallisation often occurs below the melting temperature of either pure component, setting the MAS temperature approximately 10-30°C lower than the lowest melting point helps avoid decomposition or unwanted eutectic formation. If differential scanning calorimetry (DSC) data are available, a new endothermic peak corresponding to the cocrystal can further refine this estimate. In general, the MAS temperature should fall within 60–80% of the expected cocrystal melting point, ensuring sufficient molecular mobility for cocrystal formation without crossing into the melting or degradation zone of the components. The estimated target temperature will determine the holding time at which the cocrystal is fully formed.
2. *Ramp time*. It will determine how quickly the microwave reaches the target temperature. It usually takes 2–5 minutes. Shorter ramp means faster heating, leading to more uniform activation. Longer ramp means gentler heating that avoids overheating or "hot spots" in sensitive samples. An example in determining the ramp time is heating the samples once the temperature target has been determined. For example, Pagire et al. (2013) determined their setting by heating the equal moles (0.25 mol) of each solvent alone and 0.4 mmol of caffeine, malic acid or caffeine–malic acid mixture in 0.25 mol of each solvent were subjected to microwave irradiation in 30 ml capacity glass tubes in a microwave reactor (Monowave 300, Anton Paar Gmbh, Austria). Each sample was heated to 80°C under continuous stirring at 600 rpm. Time and microwave power required to reach 80°C were noted.
3. *Hold time*. The holding time refers to the duration for which the reaction mixture is held at the target temperature after it has been reached under continuous microwave irradiation. Once the target temperature is determined, we must observe whether it can promote cocrystal formation and how long it takes. Thus, we need to optimise the holding time. A good starting point to optimise the hold time range would be 1–10 minutes at the temperature target. For example, start with a 1-minute holding time. Then, cocrystal formation will be observed using PXRD, DSC, FTIR, and/or direct visual observation. Further, we can adjust based on the results (e.g., incomplete conversion or degradation signs). At this stage, we can adjust the temperature to raise or lower it.
4. *Microwave exposure mode*. Exposure mode can be continuous or pulsed. Both continuous and pulsed microwave irradiation modes can be used for cocrystal synthesis. The limitations for their selection depend on the thermal sensitivity of the cocrystal components to temperature exposure. Continuous irradiation provides rapid and continuous heating, making it suitable for systems that can stabilise at high temperatures on a sustained basis. Previous experience with the kinetics of cocrystal synthesis using a particular material can also be decisive, as it will help determine the intensity of radiation exposure and the desired heating profile. However, pulsed irradiation offers greater thermal control by delivering energy in short bursts, which helps minimise the risk of degradation for thermally sensitive compounds.
5. *Stirring speed*. It will control homogeneity and contact between components. The proper stirring in MAS will also prevent a hot spot in the reaction vessel. 400–800 rpm is preferred for most slurries and suspensions, and 0 rpm is preferred if neat-MAS is used (no solvent). As a rule, use higher stirring for high-viscosity samples or slurries.

10.2 Potential Troubleshooting Issues

Using microwave-assisted synthesis might encounter some issues. Below are possible issues and the troubleshooting:

1. *Incomplete cocrystal formation*. The possible cause might be insufficient heating time or temperature. Material properties, such as poor molecular diffusion in the solid-state method or incorrect molar ratio, can be the cause. These issues can be addressed by increasing heating time in small increments (e.g., an additional 2–5 min), using solvent-assisted MAS to improve diffusion, and confirming a stoichiometric ratio (1:1 or 1:2).
2. *Decomposition*. The possible cause might be excessive microwave power and prolonged holding time. These issues can be addressed by reducing microwave power and shortening microwave pulses (e.g., 30 sec ON, 30 sec OFF).
3. *Poor cocrystal yield or low purity*. The possible cause might be the presence of unreacted starting materials. These issues can be addressed by optimising temperature, holding time, and solvent choice (e.g., ethanol helps control

nucleation) or by trying alternative synthesis techniques (e.g., solution evaporation if solid-state fails).

11. CONCLUSIONS

Microwave-assisted synthesis offers a fast, energy-efficient, and environmentally sustainable alternative for pharmaceutical cocr ystal production. It enhances molecular diffusion and interaction through dielectric heating, leading to efficient noncovalent bonding. Compared to conventional methods, MAS reduces solvent consumption, shortens synthesis time, and yields high-purity products. Yet, its industrial application is still emerging. Future research should focus on process optimization, integration with quality-by-design (QbD) strategies, and development of continuous flow microwave reactors. MAS holds promise for drug repurposing and extending drug lifecycles, presenting a strategic advantage in pharmaceutical innovation. With increasing emphasis on green manufacturing, MAS represents a forward-thinking platform for modern drug formulation as well as drug safety.

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