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Review Article

Applications, Case Studies, Limitations, and Future Perspectives

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Microwave-assisted synthesis (MAS) has emerged as one of the most transformative enabling technologies in modern pharmaceutical chemistry. By coupling electromagnetic energy directly with the dipoles and ions of a reaction medium, microwave dielectric heating achieves rapid, volumetric, and highly reproducible heating that routinely compresses reaction times from hours or days to minutes or even seconds, while frequently improving yield, purity, and selectivity relative to conventional conductive heating. This review presents a comprehensive account of the scientific principles underlying microwave dielectric heating, the instrumentation used in monomode and multimode reactors, and the rationale for adopting MAS as a green-chemistry platform across the pharmaceutical value chain. Applications spanning active pharmaceutical ingredient (API) and heterocyclic scaffold synthesis, pharmaceutical cocrystals, solid dispersions and in situ amorphization for bioavailability enhancement, nanocarrier and nanocomposite drug-delivery systems, green synthesis of antimicrobial metal nanoparticles, and continuousflow microwave processing for industrial scale-up are critically discussed. Representative case studies-including microwave-induced solid dispersions of glipizide and atorvastatin, cyclodextrin nanosponges of domperidone, microwave-assisted heterocyclic drug-discovery libraries, green silver-nanoparticle synthesis, and commercial continuous-flow microwave reactors-illustrate the translational impact of the technology. The review also critically examines the limitations of MAS, including penetration-depth constraints, scale-up non-uniformity, thermalrunaway and safety concerns, high capital cost, and the persistent ambiguity surrounding non-thermal ('specific') microwave effects. Finally, emerging directions are outlined, including hybrid microwave-flow platforms, process analytical technology (PAT)-integrated continuous manufacturing, artificial-intelligence-guided reaction optimisation, and microwave-enabled personalised and sustainable drug manufacturing. Collectively, the evidence indicates that microwave technology, when rationally engineered and validated, offers a scientifically robust and industrially viable route toward faster, greener, and more efficient pharmaceutical synthesis and formulation.

Keywords: microwave-assisted synthesis, dielectric heating, green chemistry, pharmaceutical cocrystals, solid dispersion, nanocarriers, continuous-flow synthesis, drug discovery

INTRODUCTION

Heat has always been central to synthetic chemistry, and for nearly a century and a half the Bunsen burner, oil bath, heating mantle, and hot plate dominated the laboratory as the principal means of driving chemical transformations. The introduction of domestic microwave ovens into synthetic laboratories in 1986 by Gedye et al. [1] marked a paradigm shift: microwave irradiation was shown to dramatically accelerate simple organic transformations relative to conventional reflux conditions. Over the subsequent two decades, the development of dedicated, pressure- and temperature-controlled laboratory microwave reactors transformed this initial curiosity into an established mainstream synthetic technique, comprehensively reviewed by Kappe and co-workers [1,5,6] and by de la Hoz, Díaz-Ortiz and Moreno [3].

Within pharmaceutical sciences specifically, microwave-assisted synthesis (MAS) has found application at almost every stage of the drug life cycle: from the rapid generation and optimisation of lead compounds and combinatorial libraries in early discovery [7,10], through process chemistry and scale-up of active pharmaceutical ingredients (APIs) [17-19], to downstream pharmaceutical formulation strategies such as cocrystal engineering, solid-dispersion-based bioavailability enhancement, and nanocarrier fabrication [22-30]. The unifying scientific rationale is dielectric heating: unlike conductive heating, which relies on heat transfer from a hot vessel wall inward, microwave energy couples directly with polar molecules and mobile ions throughout the bulk of the reaction mixture, producing rapid, relatively uniform, and highly controllable in-core heating [3,4].

This confluence of speed, energy efficiency, improved reproducibility, and compatibility with green and solvent-minimised protocols has made MAS particularly attractive to the pharmaceutical industry, where reaction telescoping, process intensification, and sustainability metrics are of growing regulatory and commercial importance [20,21]. The present review synthesises the scientific principles of microwave dielectric heating, surveys its major pharmaceutical applications, presents illustrative case studies drawn from the peer-reviewed literature, and critically evaluates the limitations and future trajectory of the technology as a platform for next-generation pharmaceutical synthesis and manufacturing.

2. Principles of Microwave-Assisted Synthesis

2.1 Dielectric Heating Mechanism

Microwaves occupy the electromagnetic spectrum between infrared radiation and radiofrequency waves (approximately 300 MHz-300 GHz); laboratory and domestic microwave reactors conventionally operate at 2.45 GHz to avoid interference with telecommunication bands. At this frequency, microwave energy is absorbed by a reaction medium through two principal mechanisms: dipolar polarisation, in which permanent or induced molecular dipoles attempt to realign with the rapidly oscillating electric field and lose energy as heat through molecular friction and dielectric loss, and ionic conduction, in which dissolved ions oscillate under the field and dissipate kinetic energy through collisions [3,4]. The efficiency with which a given solvent or reagent converts absorbed microwave energy into heat is quantified by the loss tangent ($\tan \delta = \varepsilon''/\varepsilon'$, where ε'' is the dielectric loss and ε' is the dielectric constant); solvents such as water, ethanol, dimethyl sulfoxide, and ionic liquids possess high $\tan \delta$ values and heat efficiently, whereas non-polar solvents such as hexane or toluene are essentially microwave-transparent [1,3].

Because energy is delivered directly and simultaneously throughout the irradiated volume rather than diffusing inward from a heated vessel wall, microwave heating produces an inverted temperature gradient relative to conductive oil-bath heating: the bulk of the reaction mixture heats rapidly while the vessel wall itself remains comparatively cool, minimising wall effects, decomposition, and hot-spot-induced side reactions when appropriately controlled [1]. This volumetric, in-core heating mode explains the frequently observed rate accelerations, cleaner reaction profiles, and improved reproducibility relative to conventional heating [3,4].

2.2 Thermal versus Non-Thermal ('Specific') Microwave Effects

A long-standing debate in the microwave-chemistry literature concerns whether rate enhancements arise purely from superheating, rapid bulk heating, and the elimination of wall effects (thermal/kinetic effects), or whether a genuine non-thermal 'specific microwave effect'-arising from direct field-molecule interactions that lower the effective activation energy or alter pre-exponential factors-also contributes [3,4]. Perreux and Loupy [4] proposed a mechanistic rationalisation linking the magnitude of observed microwave effects to the polarity of the reaction medium and the mechanism of the transition state, while Kappe [1,5] has argued that most reported 'non-thermal' effects can be rationalised once accurate internal temperature measurement (by fibre-optic or infrared sensing) and adequate stirring are ensured. For the purposes of pharmaceutical process development, both camps agree that precise, reproducible internal-temperature control-rather than the semantic question of thermal versus non-thermal origin-is the critical determinant of a robust, scalable microwave protocol [1,8].

2.3 Instrumentation: Monomode and Multimode Reactors

Two broad classes of dedicated laboratory microwave reactor are in routine pharmaceutical use. Monomode (single-mode) reactors focus microwave energy into a small, well-defined cavity containing a single reaction vessel (typically 0.5-50 mL), producing a highly reproducible and intense electromagnetic field suitable for reaction optimisation, high-throughput library synthesis, and mechanistic study [1,7]. Multimode reactors distribute microwave energy across a larger, mode-stirred cavity capable of accommodating multiple vessels or larger reaction volumes (tens to hundreds of millilitres), and are more commonly employed for parallel synthesis and preliminary scale-up [1,6]. Both platforms are equipped with sealed-vessel technology permitting superheating of solvents well above their atmospheric boiling points, along with in situ infrared or fibre-optic temperature sensing, pressure monitoring, and programmable power/temperature ramps that together provide the reproducibility demanded by regulated pharmaceutical process development [1,5].

2.4 Comparative Advantages over Conventional Conductive Heating

Relative to oil-bath, heating-mantle, or steam-jacketed conductive heating, microwave dielectric heating in pharmaceutical contexts is consistently reported to offer: (i) dramatic reductions in reaction time, often from hours to minutes [1,2]; (ii) improved yields and purity through suppression of thermal decomposition pathways and wallcatalysed side reactions [9,11]; (iii) enhanced reproducibility owing to precise, closed-loop temperature/power control [1]; (iv) compatibility with solvent-free, aqueous, or otherwise benign reaction media, supporting greenchemistry objectives [11,16]; and (v) narrower, more uniform particle-size distributions when applied to nanomaterial and nanocarrier synthesis, owing to rapid and homogeneous nucleation [12,13].

3. Rationale for Microwave Technology in Pharmacy

3.1 Green Chemistry and Process Intensification

The pharmaceutical industry has historically been criticised for high process-mass-intensity and solvent waste; fine-chemical and pharmaceutical manufacturing routinely generates some of the highest E-factors (kg waste per kg product) among chemical sectors [20]. Microwave technology directly addresses several of the twelve principles of green chemistry by enabling solvent-free or aqueous-phase reactions, reducing energy consumption through shorter cycle times and direct volumetric heating, and improving atom economy through cleaner reaction profiles that reduce downstream purification burden [11,16,20]. These attributes have made MAS a preferred platform for 'process intensification' initiatives aimed at telescoping multiple synthetic steps, minimising intermediate isolation, and reducing overall manufacturing footprint [17,21].

3.2 Relevance Across the Drug Development Life Cycle

MAS is not confined to a single stage of pharmaceutical development. In early discovery, monomode microwave reactors accelerate hit-to-lead optimisation and combinatorial/parallel library synthesis, permitting medicinal chemists to explore structure-activity relationships in days rather than weeks [7,10,15]. In process chemistry, microwave methods are used for route scouting, rapid reaction-condition screening, and-when coupled with continuous-flow technology-scale-up to pilot and manufacturing volumes [17-19,21]. In formulation science, microwave irradiation is applied downstream of API synthesis to engineer solid-state forms (cocrystals, amorphous solid dispersions), functionalised excipient complexes (cyclodextrin nanosponges), and nanocarrier delivery systems that directly address the biopharmaceutical challenge of poor aqueous solubility affecting an estimated 40% or more of new chemical entities [22-30].

4. Applications of Microwave-Assisted Synthesis in Pharmaceutical Sciences

4.1 Synthesis of Active Pharmaceutical Ingredients and Bioactive Heterocyclic Scaffolds

Nitrogen- and oxygen-containing heterocycles-including pyrazoles, pyrimidines, quinolines, coumarins, isatins, and pyrazolopyrimidines-constitute the structural core of a large proportion of marketed drugs. Tiwari et al. [14] comprehensively reviewed microwave-assisted organic synthesis

(MAOS) routes to these scaffolds, highlighting catalyst-free, regioselective protocols that deliver good-to-excellent yields (70-92%) within minutes under microwave irradiation, compared with hours or days under conventional reflux. Similarly, Henary et al. [15] reviewed the synthesis of small- and medium-sized nitrogen heterocycles-pyrroles, indoles, pyridines, imidazoles, pyrazoles, and 1,2,3-triazoles-emphasising the compatibility of MAOS with combinatorial medicinal-chemistry workflows. Gawande et al. [12] further demonstrated that solid-supported catalysts (e.g., Nafion NR50) and aqueous reaction media can be combined with microwave heating to generate pharmaceutically relevant oxadiazoles, thiadiazoles, dioxanes, pyrazoles, hydrazones, and dihydropyrimidinones under fully green conditions. McConnell et al. [16] extended this approach to transition-metal-, ligand-, and organic-solvent-free synthesis of anilines, phenols, and benzenediamines-key building blocks for pharmaceutical intermediates-directly from activated aryl halides.

4.2 Pharmaceutical Cocrystals

Cocrystal engineering has become a mainstream strategy for modulating the solubility, dissolution rate, physical stability, and mechanical properties of active pharmaceutical ingredients without altering their covalent structure. Microwave-assisted synthesis offers a rapid, solvent-minimised alternative to slurry crystallisation, solvent evaporation, and mechanochemical grinding for cocrystal formation, typically achieving comparable or superior yield, purity, and crystallinity within a fraction of the processing time. Systematic literature reviews conducted under PRISMA guidelines have concluded that microwave-assisted cocrystallisation is a scalable and reproducible green alternative for enhancing the solubility, dissolution, stability, and bioavailability of poorly soluble APIs, while reducing solvent consumption relative to conventional cocrystal-screening approaches.

4.3 Solid Dispersions and In Situ Amorphisation for Bioavailability Enhancement

A substantial and growing body of pharmaceutical literature documents the use of microwave irradiation to prepare amorphous or partially amorphous solid dispersions of poorly water-soluble Biopharmaceutics Classification System (BCS) class II drugs. Isaac et al. [22] demonstrated that microwave-induced melt mixing of glipizide with polyethylene glycol 4000 produced a more homogeneous, glass-transparent dispersion than conventional heating, with confirmed polymorphic transformation and a 153.7% relative increase in oral bioavailability in a rabbit pharmacokinetic model. Kushare and Gattani [23] independently developed microwave-generated bionanocomposites of glipizide using natural gum carriers, achieving comparable solubility and dissolution enhancement. Maurya et al. [24] applied microwave-induced diffusion to atorvastatin calcium, while Alshehri et al. [25] used solvent-free microwave irradiation to prepare solid dispersions of mefenamic and flufenamic acid with markedly improved in vitro dissolution and in vivo anti-inflammatory activity. Earlier work by Moneghini et al. [26] similarly established microwave-generated solid dispersion of ibuprofen as a viable alternative to fusion or solventevaporation methods. More recently, Hempel et al. [27] showed that microwave radiation can be used to amorphise a crystalline drug in situ within the final dosage form, offering a strategy to circumvent the physical-stability problems that typically plague amorphous solid dispersions manufactured upstream by hot-melt extrusion or spray drying.

4.4 Nanocarriers, Nanocomposites, and Drug-Delivery Systems

Microwave-assisted synthesis has been extensively applied to the fabrication of nano- and micro-scale drug carriers, including polymeric, lipidic, metallic, and cyclodextrin-based systems. Vij et al. [28] used a Box-Behnken design to optimise microwave power, response speed, and stirring speed for the synthesis of β-cyclodextrin nanosponges loaded with domperidone, achieving a 77.4% product yield, a particle size of 195.7 nm, and 84% drug entrapment efficiency, with improved dissolution relative to the free drug. Singireddy et al. [29] directly compared microwave-assisted and conventional heating for cyclodextrin nanosponge synthesis, confirming superior efficiency and reduced processing time for the microwave route. Virlley et al. [30] comprehensively reviewed microwaveassisted nanocarrier-based drug-delivery platforms, noting that dipolar polarisation and ionic conduction jointly enable rapid, uniform nucleation and narrower particle-size distributions relative to

conventional co-precipitation or emulsification methods, benefiting lipidic, polymeric, metallic, and micellar nanoparticle systems alike.

4.5 Green Synthesis of Metal Nanoparticles for Antimicrobial and Biomedical Applications

Microwave-assisted green synthesis has become a preferred route for producing biogenic silver nanoparticles (AgNPs) using plant, algal, fungal, or agricultural-waste extracts as reducing and stabilising agents, avoiding toxic chemical reductants. Nadagouda et al. [13] established the foundational methodology for microwave-assisted green synthesis of silver and other metal nanostructures using biodegradable polyols and plant-derived agents. Building on this platform, Anis et al. [31] synthesised AgNPs from pineapple leaf waste under microwave-assisted extraction, obtaining hexagonal, spherical nanoparticles (40-150 nm) with superior antimicrobial activity against Escherichia coli, Bacillus subtilis, and Staphylococcus aureus relative to non-microwave-assisted synthesis. Eshghi et al. [32] used Juglans regia leaf extract under microwave irradiation, optimised by response-surface methodology, to produce AgNPs with strong bactericidal activity against both Gram-negative and Gram-positive organisms. Most recently, Magdy and Belal [33] reported an ultrafast (30-second) microwave-assisted green synthesis of AgNPs using Lupinus albus seed extract, which were subsequently applied as fluorescent nanosensors for the sensitive determination of the drugs entacapone and thiopental in human plasma and pharmaceutical dosage forms-illustrating the dual synthetic and analytical utility of microwave-derived nanomaterials in pharmacy.

4.6 Continuous-Flow Microwave Processing and Industrial Scale-Up

A persistent challenge for translating laboratory-scale microwave chemistry to pharmaceutical manufacturing has been the limited penetration depth of microwave radiation into large reaction volumes. Continuous-flow microwave reactors address this constraint by passing a thin stream of reaction mixture through a microwaveirradiated zone, decoupling irradiated volume from total batch size. Bergamelli et al. [18] evaluated a commercially available continuous-flow microwave reactor across six pharmaceutically relevant reaction types, achieving production rates of 0.5-3.0 mol/h with minimal redevelopment of the underlying chemistry. Damm et al. [19] demonstrated that high-temperature microwave chemistry developed at milligram-to-gram scale in sealed vessels could be translated directly to scalable continuous-flow processes without significant re-optimisation. Sadler et al. [17] reviewed the synergistic combination of microwave and continuous-flow platforms in drug discovery and candidate development, including applications in radiopharmaceutical preparation, while Porta et al. [21] and Watson [20] discuss the broader adoption of flow chemistry-of which microwave-flow is a key enabling variant-across fine-chemical and pharmaceutical manufacturing, citing regulatory approval of several continuously manufactured pharmaceutical products as evidence of industrial maturity.

5. Case Studies

The following case studies, drawn directly from the peer-reviewed pharmaceutical literature, illustrate the practical translation of the principles described above into measurable pharmaceutical outcomes.

Case Study 1: Microwave-Induced Solid Dispersion of Glipizide

Isaac et al. [22] compared microwave (MW) irradiation with conventional heating (CH) for preparing solid dispersions of the poorly water-soluble antidiabetic drug glipizide with polyethylene glycol 4000. Chemical stability of glipizide following MW exposure was confirmed by HPLC, FT-IR, 1H-NMR, and mass spectrometry. MWassisted melt mixing produced a more homogeneous, glass-transparent dispersion than CH, with powder X-ray diffraction confirming a polymorphic transformation of the drug. In a comparative rabbit pharmacokinetic study, sustained-release tablets prepared from the MW-solid dispersion showed a relative bioavailability of 153.7% versus the conventional-heating dispersion, and solubility in pH 6.8 phosphate buffer increased from 46 to 72.25 µg/mL. This case exemplifies how microwave-induced polymorphic transformation, rather than simple particle-size reduction, can be the principal mechanism underlying bioavailability enhancement.

Case Study 2: Atorvastatin Calcium Solubility Enhancement

Maurya et al. [24] applied a microwave-induced diffusion technique to atorvastatin calcium, a widely prescribed BCS class II statin, using hydrophilic carriers to generate a bio-nanocomposite dispersion. The microwave-processed formulation exhibited significantly improved aqueous solubility and in vitro dissolution relative to both the pure drug and conventionally prepared physical mixtures, attributable to microwave-induced disruption of the drug's crystal lattice and its homogeneous molecular-level dispersion within the hydrophilic carrier matrix.

Case Study 3: Cyclodextrin-Based Nanosponges for Domperidone

Vij et al. [28] addressed the low oral bioavailability of domperidone, a BCS class II antiemetic, by synthesising βcyclodextrin-based nanosponges using a microwave-assisted, Box-Behnken-optimised protocol. Microwave power level, reaction (response) speed, and stirring speed were systematically varied; the optimal batch achieved a 77.4% product yield, particle size of 195.68 ± 2.16 nm, drug entrapment efficiency of 84 ± 4.2%, and zeta potential of −9.17 ± 0.43 mV. FTIR, DSC, and XRD confirmed successful drug entrapment, while SEM revealed the characteristic porous nanosponge morphology. In vitro release studies demonstrated significantly enhanced drug release from the microwave-synthesised nanosponges relative to the plain drug, and the authors concluded that the microwave route was both faster and more solvent-sparing than conventional emulsion-solvent-diffusion methods.

Case Study 4: Microwave-Assisted Heterocyclic Scaffold Libraries for Drug Discovery

Tiwari et al. [14] catalogued a wide range of microwave-assisted routes to nitrogen- and oxygen-containing heterocycles of direct medicinal-chemistry relevance, including Suzuki-Miyaura cross-coupling, Friedländer synthesis, copper-catalysed multicomponent reactions, and catalyst-free coumarin syntheses. Reaction times were consistently compressed from hours to minutes, with several transformations proceeding in a regioselective, catalystfree manner in yields of 70-92%. This class of application demonstrates the particular value of monomode microwave reactors for rapid analogue generation and structure-activity-relationship exploration during early-stage drug discovery [7,10,15].

Case Study 5: Microwave-Assisted Green Synthesis of Antimicrobial Silver Nanoparticles

Anis et al. [31] synthesised silver nanoparticles from pineapple leaf agricultural waste using microwave-assisted extraction as a green, cost-effective alternative to chemical reduction. Optimisation of silver nitrate concentration, incubation time, and extract volume yielded hexagonal, spherical AgNPs of 40-150 nm, confirmed by UV-Vis spectroscopy, FE-SEM, FTIR, and XRD. Microwave-assisted AgNPs exhibited significantly greater antimicrobial activity against E. coli, B. subtilis, and S. aureus than nanoparticles produced without microwave assistance, with a minimum inhibitory concentration of 60 µg/mL, illustrating how microwave-induced rapid, uniform nucleation can directly translate into enhanced pharmacological performance.

Case Study 6: Commercial Continuous-Flow Microwave Reactors for Pharmaceutical Scale-Up

Bergamelli et al. [18] evaluated a commercially available continuous-flow microwave reactor (FlowSYNTH) across six pharmaceutically relevant reactions with diverse physical parameters, scaling conditions directly from tube- or batch-scale microwave optimisation with minimal redevelopment. Five of the six reactions were successfully scaled to production rates of 0.5-3.0 mol/h (1-6 L/h), and energy-consumption measurements confirmed the processefficiency advantages of the continuous-flow microwave format. This case study demonstrates a practical, industrially validated pathway for translating laboratory microwave discoveries into kilogram-scale pharmaceutical manufacturing.

6. Limitations and Challenges

Despite its considerable advantages, microwave-assisted synthesis is subject to several well-documented limitations that must be addressed for robust pharmaceutical application.

Limited penetration depth: Microwave radiation penetrates most reaction media to a depth of only a few centimetres before substantial attenuation occurs, restricting the volume that can be uniformly and effi-

ciently irradiated in a single batch reactor and complicating direct scale-up from laboratory to manufacturing volumes [18,19].

Non-uniform field distribution and scale-up unpredictability: Multimode cavities in particular can generate uneven electromagnetic field distributions, producing localised hotspots, inconsistent heating, and batch-to-batch variability that becomes more pronounced as reactor volume increases, necessitating careful reactor and vesselgeometry design [18,19].

Safety and process-hazard concerns: Sealed-vessel microwave reactions conducted above atmospheric boiling point generate significant internal pressure; rapid, uncontrolled heating of strongly microwave-absorbing or exothermic mixtures can precipitate thermal runaway, vessel rupture, or arcing, particularly with metal-containing or highly polar reagents, requiring dedicated pressure-relief and safety engineering [1].

High capital and maintenance cost: Dedicated pharmaceutical-grade microwave reactors with integrated temperature/pressure monitoring, safety interlocks, and continuous-flow capability represent a substantially higher capital investment than conventional heating equipment, which can be a barrier for smaller manufacturers and academic laboratories.

Solvent and reagent compatibility constraints: Reaction media with low dielectric loss (non-polar solvents) couple poorly with microwave energy and may require the addition of polar co-solvents, ionic liquids, or passive heating elements (susceptors), complicating direct translation of existing synthetic routes [3,4].

Persistent mechanistic ambiguity: Despite extensive investigation, the relative contribution of genuine nonthermal ('specific') microwave effects versus purely thermal/kinetic phenomena remains incompletely resolved for some reaction classes, complicating rational process design and occasionally leading to irreproducible claims in the literature when internal temperature is not rigorously monitored [3,4].

Regulatory and validation burden: As with any novel process technology, pharmaceutical manufacturers must generate substantial process-validation, impurity-profiling, and equivalence data to satisfy regulatory expectations (e.g., ICH Q8-Q11) before microwave-based unit operations can be incorporated into a marketed product's approved manufacturing process, which can slow industrial adoption relative to the pace of academic publication.

7. Future Scope

Several converging trends suggest that microwave technology will play an expanding role in pharmaceutical science over the coming decade.

Hybrid microwave-continuous-flow manufacturing: Building on the demonstrated scalability of commercial continuous-flow microwave reactors [17-19], increasing integration of microwave heating with continuous manufacturing platforms is expected, enabling telescoped multistep API synthesis with real-time process analytical technology (PAT) monitoring and reduced intermediate isolation [21].

Microwave-assisted personalised and on-demand manufacturing: The compact footprint and rapid cycle times of microwave reactors make them attractive candidates for small-batch, point-of-care, or on-demand synthesis of radiopharmaceuticals and personalised dosage forms, an application area already highlighted for radiopharmaceutical preparation [17].

Data-driven and AI-guided reaction optimisation: The high reproducibility and rapid iteration cycles achievable with monomode microwave reactors make them well suited to integration with automated experimentation platforms and machine-learning-guided design-of-experiments approaches, accelerating both route scouting and formulation optimisation (as exemplified by the Box-Behnken optimisation strategies already applied to nanosponge synthesis [28]).

Expansion into biologics-adjacent and green nanomedicine applications: Continued development of microwave-assisted green synthesis of metal and metal-oxide nanoparticles [13,31-33] is likely to extend into targeted nanomedicine, antimicrobial coatings, and biosensor-integrated diagnostic-therapeutic (theranostic) platforms, particularly as sustainability pressures favour plant- and waste-derived reducing agents over conventional chemical reductants.

Advanced reactor engineering to overcome penetration-depth limits: Novel waveguide, applicator, and multivessel array designs are under active development to mitigate the fundamental penetration-depth constraint of microwave radiation, potentially enabling true kilogram- to tonne-scale microwave manufacturing without loss of field homogeneity [18,19].

Deeper mechanistic characterisation: Continued application of in situ spectroscopic and computational methods to resolve the thermal/non-thermal microwave-effect debate [3,4] will support more rational, first-principles process design rather than empirical optimisation, further improving the reliability and regulatory acceptability of microwave-based pharmaceutical processes.

CONCLUSION

Microwave-assisted synthesis has evolved from a laboratory curiosity into a scientifically well-characterised and industrially validated platform technology spanning the entire pharmaceutical value chain, from API discovery and process chemistry to solid-state formulation engineering and nanomedicine. The underlying principle-direct, volumetric dielectric heating through dipolar polarisation and ionic conduction-confers well-documented advantages in reaction speed, yield, purity, reproducibility, and compatibility with green-chemistry objectives, as demonstrated across the heterocyclic synthesis, cocrystal, solid-dispersion, nanocarrier, and metal-nanoparticle case studies reviewed here. Nevertheless, penetration-depth limitations, scale-up non-uniformity, safety considerations, and residual mechanistic ambiguity around non-thermal effects continue to constrain unrestricted industrial adoption. The emergence of validated continuous-flow microwave reactors, hybrid microwave-flow manufacturing platforms, and data-driven optimisation strategies indicates a clear and scientifically grounded trajectory toward broader, more robust pharmaceutical application of microwave technology in the years ahead.

REFERENCES

1. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed. 2004;43 (46):6250-6284.
2. Gedye R, Smith F, Westaway K, Ali H, Baldisera L, Laberge L, Rousell J. The use of microwave ovens for rapid organic synthesis. Tetrahedron Lett. 1986;27 (3):279-282.
3. de la Hoz A, Díaz-Ortiz A, Moreno A. Microwaves in organic synthesis. Thermal and non-thermal microwave effects. Chem Soc Rev. 2005;34 (2):164-178.
4. Perreux L, Loupy A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. Tetrahedron. 2001;57 (45):9199-9223.
5. Kappe CO. Microwave dielectric heating in synthetic organic chemistry. Chem Soc Rev. 2008;37 (6):1127-1139.
6. Kappe CO, Dallinger D. Controlled microwave heating in modern organic synthesis: highlights from the 2004-2008 literature. Mol Divers. 2009;13 (2):71-193.
7. Kappe CO, Dallinger D. The impact of microwave synthesis on drug discovery. Nat Rev Drug Discov. 2006;5 (1):51-63.
8. Rodríguez AM, Prieto P, de la Hoz A, Díaz-Ortiz Á, Martín DR, García JI. Influence of polarity and activation energy in microwaveassisted organic synthesis (MAOS). ChemistryOpen. 2015;4 (3):308-317.
9. Larhed M, Moberg C, Hallberg A. Microwave-accelerated homogeneous catalysis in organic chemistry. Acc Chem Res. 2002;35 (9):717-727.
10. Lew A, Krutzik PO, Hart ME, Chamberlin AR. Increasing rates of reaction: microwave-assisted organic synthesis for combinatorial chemistry. J Comb Chem. 2002;4 (2):95-105.
11. Polshettiwar V, Varma RS. Microwave-assisted organic synthesis and transformations using benign reaction media. Acc Chem Res. 2008;41 (5):629-639.
12. Gawande MB, Shelke SN, Zboril R, Varma RS. Microwave-assisted chemistry: synthetic applications for rapid assembly of nanomaterials and organics. Acc Chem Res. 2014;47 (4):1338-1348.
13. Nadagouda MN, Speth TF, Varma RS. Microwave-assisted green synthesis of silver nanostructures. Acc Chem Res. 2011;44 (7):469-478.
14. Tiwari G, Khanna A, Mishra VK, Sagar R. Recent developments on microwave-assisted organic synthesis of nitrogen- and oxygencontaining preferred heterocyclic scaffolds. RSC Adv. 2023;13 (47):32858-32892.

15. Henary M, Kananda C, Rotolo L, Savino B, Owens EA, Cravotto G. Benefits and applications of microwave-assisted synthesis of nitrogen containing heterocycles in medicinal chemistry. RSC Adv. 2020;10 (24):14170-14197.
16. McConnell N, Frett B, Li H. Microwave-assisted green synthesis of anilines, phenols, and benzenediamines without transition metals, ligands, or organic solvents. Green Chem Lett Rev. 2018;11 (3):258-265.
17. Sadler S, Moeller AR, Jones GB. Microwave and continuous flow technologies in drug discovery. Expert Opin Drug Discov. 2012;7 (12):1107-1128.
18. Bergamelli F, Iannelli M, Marafie JA, Moseley JD. A commercial continuous flow microwave reactor evaluated for scale-up. Org Process Res Dev. 2010;14 (4):926-930.
19. Damm M, Glasnov TN, Kappe CO. Translating high-temperature microwave chemistry to scalable continuous flow processes. Org Process Res Dev. 2010;14 (1):215-224.
20. Watson WJW. How do the fine chemical, pharmaceutical, and related industries approach green chemistry and sustainability? Green Chem. 2012;14 (2):251-259.
21. Porta R, Benaglia M, Puglisi A. Flow chemistry: recent developments in the synthesis of pharmaceutical products. Org Process Res Dev. 2016;20 (1):2-25.
22. Isaac J, Kaity S, Ganguly S, Ghosh A. Microwave-induced solid dispersion technology to improve bioavailability of glipizide. J Pharm Pharmacol. 2013;65 (2):219-229.
23. Kushare SS, Gattani SG. Microwave-generated bionanocomposites for solubility and dissolution enhancement of poorly watersoluble drug glipizide: in-vitro and in-vivo studies. J Pharm Pharmacol. 2013;65 (1):79-93.
24. Maurya DB, Belgamwar VS, Tekade AR. Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium. J Pharm Pharmacol. 2010;62 (11):1599-1606.
25. Alshehri S, Shakeel F, Ibrahim M, Elzayat E, Altamimi M, Shazly G, Mohsin K, Alkholief M, Alsulays B, Alshetaili A, et al. Influence of the microwave technology on solid dispersions of mefenamic acid and flufenamic acid. PLoS One. 2017;12 (7):e0182011.
26. Moneghini M, Bellich B, Baxa P, Princivalle F. Microwave generated solid dispersion containing ibuprofen. Int J Pharm. 2008;361 (1-2):125-130.
27. Hempel N, Knopp MM, Berthelsen R, Löbmann K. Convection-induced vs. microwave radiation-induced in situ drug amorphization. Molecules. 2020;25 (5):1068.
28. Vij M, Dand N, Kumar L, Wadhwa P, Wani SUD, Mahdi WA, Alshehri S, Alam P, Shakeel F. Optimisation of a greener-approach for the synthesis of cyclodextrin-based nanosponges for the solubility enhancement of domperidone, a BCS class II drug. Pharmaceuticals (Basel). 2023;16 (4):567.
29. Singireddy A, Pedireddi SR, Nimmagadda S, Subramanian S. Beneficial effects of microwave assisted heating versus conventional heating in synthesis of cyclodextrin based nanosponges. Mater Today Proc. 2016;3 (10):3951-3959.
30. Virlley S, Shukla S, Arora S, Shukla D, Nagdiya D, Bajaj T, Kujur S, Garima, Kumar A, Bhatti JS, Singh A, Singh C. Recent advances in microwave-assisted nanocarrier-based drug delivery systems: trends and technologies. J Drug Deliv Sci Technol. 2023;87:104842.
31. Anis SNS, Liew WC, Mohd Marsin A, Muhamad II, Teh SH, Md Khudzari AZ. Microwave-assisted green synthesis of silver nanoparticles using pineapple leaves waste. Clean Eng Technol. 2023;15:100660.
32. Eshghi M, Vaghari H, Najian Y, Najian MJ, Jafarizadeh-Malmiri H, Berenjian A. Microwave-assisted green synthesis of silver nanoparticles using Juglans regia leaf extract and evaluation of their physico-chemical and antibacterial properties. Antibiotics (Basel). 2018;7 (3):68.
33. Magdy G, Belal F. Biogenic silver nanoparticles via microwave-assisted green synthesis: antimicrobial agents and fluorescent nanosensors for the sensitive determination of entacapone and thiopental in human plasma and dosage forms. Luminescence. 2026;41 (2):e70436.

34. Wong TW, Nurjaya S. Drug release property of chitosan-pectinate beads and its changes under the influence of microwave. Eur J Pharm Biopharm. 2008;69 (1):176-188.

35. Larhed M, Hallberg A. Microwave-assisted high-speed chemistry: a new technique in drug discovery. Drug Discov Today. 2001;6 (8):406-416.

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