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MODERN GREEN HEATING APPROACHES FOR PHARMACEUTICAL APPLICATIONS: A REVIEW OF MICROWAVE AND EMERGING ALTERNATIVES

***Tapan Kumar Mahato**

Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India.

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***Corresponding Author: Tapan Kumar Mahato**

Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India.

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ABSTRACT

Conventional thermal heating used in pharmaceutical synthesis and processing often suffers from slow heat transfer, high energy consumption, solvent-intensive conditions, and unwanted by-products due to prolonged exposure to elevated temperatures. In response, green chemistry has accelerated the adoption of energy-efficient "non-classical" activation methods that improve reaction efficiency while reducing waste and environmental burden. This review discusses microwave-assisted approaches as a leading green heating technology for pharmaceutical applications, highlighting its rapid volumetric heating, shortened reaction times, cleaner conversions, and potential for solvent minimization. Beyond microwave irradiation, emerging alternatives, including ultrasound-assisted (sonochemical) activation, mechanochemical/solvent-free grinding (ball milling), photochemical/visible-light activation, electrochemical methods, and infrared-assisted heating, are critically examined for their relevance in drug substance (Active Pharmaceutical Ingredient) synthesis, intermediate preparation, crystallization/co-crystal development, and selected formulation operations. These methods often enable milder conditions, improved selectivity, reduced reagent excess, and enhanced mass transfer, supporting sustainability targets without compromising product quality. Key pharmaceutical considerations such as scalability, reproducibility, process safety, impurity control, and quality-by-design compatibility are discussed, alongside practical limitations (equipment cost, scale-up complexity, and process standardization). Overall, integrating microwave technology with newer green activation strategies offers a practical pathway to safer, faster, and more sustainable pharmaceutical development and

manufacturing, while aligning with evolving expectations for environmentally responsible drug production.

KEYWORDS: Microwave-assisted synthesis; Green chemistry; Pharmaceutical manufacturing; Ultrasound (sonochemistry); Mechanochemistry; Sustainable drug synthesis.

1. INTRODUCTION

1.1 Need for green heating technologies in pharmaceutical sciences: The pharmaceutical industry is undergoing a paradigm shift toward sustainable and environmentally benign manufacturing practices in alignment with the principles of green chemistry. Conventional thermal heating techniques such as oil baths and hot plates are energy intensive, time consuming, and often associated with poor temperature control and higher solvent consumption, which increase environmental burden and operational costs [1,2]. To overcome these limitations, advanced green heating technologies have emerged as efficient alternatives that enhance reaction kinetics, improve product yield, and reduce energy consumption and waste generation.

Microwave-assisted heating has gained significant attention as an eco-friendly approach in pharmaceutical synthesis and formulation development. Mahato (2022) comprehensively reviewed microwave heating as a green chemistry tool and highlighted its advantages, including rapid volumetric heating, reduced reaction time, enhanced selectivity, improved reproducibility, and minimized solvent usage. The study emphasized microwave technology as an effective platform for sustainable pharmaceutical processing, particularly in organic synthesis, nanoparticle preparation, and drug formulation development. However, reliance on a single heating modality may limit broader industrial adoption [3].

Recent advances have expanded green heating strategies beyond microwave technology to include ultrasound-assisted heating, infrared irradiation, ohmic heating, induction heating, supercritical fluid heating, and hybrid integrated systems. These emerging techniques offer superior process control, scalability, and energy efficiency, making them highly relevant for pharmaceutical manufacturing, continuous processing, and regulatory-compliant production environments [4,5]. Therefore, the present review extends earlier work by Mahato (2022) by systematically evaluating microwave technology alongside emerging green heating alternatives and their pharmaceutical applications [3].

1.2 Microwave heating as a green benchmark technology: Microwave-assisted heating has emerged as a prominent green technology due to its ability to provide rapid, uniform, and

volumetric heating through dipolar polarization and ionic conduction mechanisms [6,7]. Compared to conventional heating, microwave irradiation significantly reduces reaction time, improves yield, enhances selectivity, and lowers solvent requirements [8]. Microwave-assisted synthesis has been successfully applied in pharmaceutical chemistry for heterocycle formation, nucleophilic substitution reactions, crystallization, nanoparticle synthesis, and formulation development [4]. The capability of microwave systems to operate under solvent-free or minimal solvent conditions further strengthens their environmental advantages and industrial relevance [9].

1.3 Emerging alternative green heating technologies: In addition to microwave heating, several alternative green activation techniques have gained importance in pharmaceutical research. Ultrasound-assisted (sonochemical) processing improves reaction efficiency through acoustic cavitation, enhancing mass transfer and molecular collisions [10]. Mechanochemical methods enable solvent-free reactions driven by mechanical energy, offering a highly sustainable approach for pharmaceutical synthesis [11]. Photochemical activation allows selective energy input using visible light, promoting mild reaction conditions and reduced thermal degradation [12]. Infrared heating and electrochemical activation are also increasingly applied for controlled energy delivery and cleaner redox transformations in pharmaceutical manufacturing [13,14]. These emerging heating strategies collectively expand the scope of green pharmaceutical processing. Figure 1 presents a hierarchical overview of eco-friendly heating approaches, including microwave, ultrasound, infrared, radiofrequency, induction, hybrid heating, and supercritical fluid-assisted thermal systems, highlighting their application domains and sustainability advantages in pharmaceutical research and manufacturing. Figure 2 illustrates the differences in energy efficiency, processing time, solvent consumption, and environmental impact between traditional thermal methods and advanced green heating technologies, demonstrating the superior sustainability and operational efficiency of modern heating approaches.

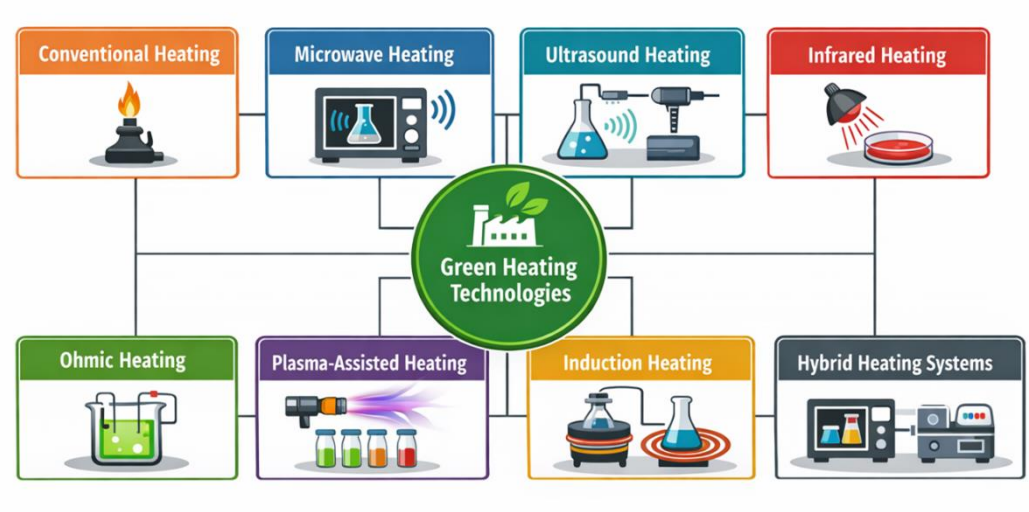

Figure 1. Classification of modern green heating technologies used in pharmaceutical and chemical processing.

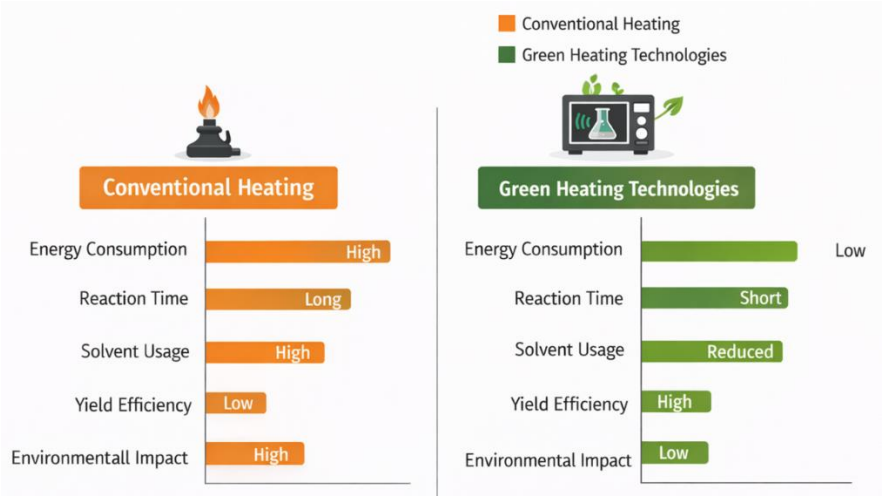

Figure 2. Comparative performance of conventional and green heating techniques in pharmaceutical processing.

Table 1. Comparative summary of green heating technologies used in pharmaceutical applications.

Heating technology	Energy source	Major pharmaceutical applications	Key advantages	Limitations	Reference
Microwave heating	Electromagnetic radiation (2.45 GHz)	API synthesis, extraction, drying, crystallization	Rapid heating, reduced reaction time, energy efficient	Scale-up challenges, equipment cost	[3,6]
Ultrasound	Acoustic	Particle size	Enhanced	Equipment	[25,10]

heating (Sonochemical)	cavitation energy	reduction, emulsification, extraction	mass transfer, lower solvent use	complexity	
Infrared heating	Radiant thermal energy	Drying, coating, sterilization	Uniform surface heating, fast response	Limited penetration depth	[21,28]
Ohmic heating	Electrical current	Sterilization, liquid formulation processing	Uniform volumetric heating, minimal thermal gradients	Requires conductive materials	[55,30]
Induction heating	Magnetic field induction	Reactor heating, metallic vessel processing	Precise temperature control, rapid heat transfer	Limited to conductive materials	[56,57]
Plasma heating	Ionized gas energy	Surface modification, sterilization	High reactivity, solvent-free processing	Technical complexity	[44,42]
Hybrid heating systems	Combined energy sources	Continuous manufacturing, scale-up processes	High efficiency, process optimization	Integration complexity	[58,59]

2. Microwave-assisted heating in pharmaceutical sciences

2.1 Principle and mechanism of microwave heating: Microwave heating is based on the interaction of electromagnetic radiation (frequency 2.45 GHz) with polar molecules and ionic species present in reaction media, resulting in rapid volumetric heating [6]. Unlike conventional conductive heating, microwave irradiation generates heat internally through dipolar polarization and ionic conduction mechanisms, enabling uniform temperature distribution and minimizing thermal gradients [9]. Dipolar polarization occurs when polar molecules attempt to align with the alternating electromagnetic field, generating frictional heat, while ionic conduction produces heat through the oscillation of charged species [7]. These mechanisms allow faster energy transfer and improved reaction kinetics compared to traditional heating approaches.

2.2 Advantages of microwave heating in pharmaceutical applications: Microwave-assisted processes offer several advantages in pharmaceutical sciences, including reduced reaction time, improved product yield, enhanced purity, and lower solvent consumption [8].

Studies have demonstrated that microwave heating significantly improves the efficiency of heterocyclic synthesis, peptide coupling reactions, crystallization processes, and nanoparticle formulation [6,4]. Additionally, microwave-assisted solid-state reactions enable solvent-free synthesis, aligning with green chemistry principles by reducing hazardous waste generation and energy consumption [1]. The ability to precisely control temperature and pressure also improves reproducibility and scalability for industrial pharmaceutical applications.

2.3 Pharmaceutical applications of microwave technology: Microwave irradiation has been widely applied across various pharmaceutical processes. In medicinal chemistry, it accelerates drug intermediate synthesis and multi-component reactions, leading to rapid lead compound development [6]. In formulation science, microwave-assisted drying improves moisture removal efficiency in granules and solid dispersions [9]. Microwave technology has also been successfully utilized for nanoparticle synthesis, polymer modification, and enhancement of drug solubility through solid dispersion techniques [8]. Furthermore, microwave-assisted extraction improves the recovery of bioactive compounds from medicinal plants with reduced solvent usage and shorter extraction time [4].

3. Ultrasound-assisted (Sonochemical) heating and processing in pharmaceutical sciences

3.1 Principle and mechanism of ultrasound heating: Ultrasound-assisted processing operates through the phenomenon of acoustic cavitation, where high-frequency sound waves (20–100 kHz) generate microscopic bubbles in liquid media that grow and collapse violently, producing localized hotspots with extremely high temperatures and pressures [10]. These transient microenvironments enhance mass transfer, improve molecular collisions, and accelerate chemical reactions without significantly increasing bulk temperature [4]. The mechanical shear forces generated during bubble collapse also promote cell disruption, particle size reduction, and improved solvent penetration, making ultrasound an efficient green alternative to conventional thermal heating techniques [15].

3.2 Advantages of ultrasound technology in pharmaceutical applications: Ultrasound-assisted processes offer several benefits, including reduced extraction time, lower energy consumption, minimal solvent requirement, and improved process efficiency [4]. Compared to traditional heating, sonochemical methods enable better control of reaction conditions and enhance yield and purity of pharmaceutical intermediates [10]. Ultrasound also facilitates mild processing conditions, which is particularly advantageous for thermolabile drugs, herbal

extracts, and biopharmaceutical products. Furthermore, ultrasound techniques support sustainable manufacturing by reducing environmental impact and operational costs [15].

3.3 Pharmaceutical applications of ultrasound-assisted processing: Ultrasound has been extensively applied in pharmaceutical extraction, nanoparticle synthesis, emulsification, crystallization, and drug delivery system development. Ultrasound-assisted extraction improves recovery of bioactive phytochemicals, alkaloids, flavonoids, and essential oils with reduced solvent consumption and shorter processing times [4]. In formulation science, ultrasound is used for nanoparticle size reduction, liposome preparation, and enhancement of drug dissolution and bioavailability [10]. Additionally, ultrasound-assisted crystallization improves crystal morphology control and polymorphic stability, which are critical for drug quality and performance [15].

4. Infrared (IR) heating technology in pharmaceutical processing

4.1 Principle and mechanism of infrared heating: Infrared heating is based on the direct transfer of electromagnetic radiation energy (wavelength range 0.78–1000 μm) to materials, where it is absorbed and converted into thermal energy at the molecular level [16]. Unlike conventional conduction or convection heating, infrared radiation penetrates the surface layer and excites molecular vibrations, resulting in d and uniform heating [17]. This mechanism minimizes heat loss to the surrounding environment and significantly improves energy efficiency. Studies have demonstrated that IR heating reduces processing time and achieves faster moisture removal and thermal activation compared to traditional hot-air systems [18].

4.2 Advantages of infrared heating in pharmaceutical applications: Infrared heating offers multiple advantages, including shorter heating cycles, lower energy consumption, improved temperature control, and reduced thermal degradation of active pharmaceutical ingredients (APIs) [16]. The non-contact nature of IR heating decreases contamination risk and supports hygienic pharmaceutical manufacturing practices [17]. Additionally, infrared systems allow selective heating of materials without excessive heating of equipment surfaces, making them suitable for continuous processing and scale-up operations. These attributes align strongly with green chemistry principles by minimizing waste generation and improving overall process sustainability [18].

4.3 Pharmaceutical applications of infrared heating: Infrared heating has been applied in pharmaceutical drying, granulation, coating, sterilization, and thermal treatment of powders and tablets. IR-assisted drying improves moisture removal efficiency while preserving drug stability and content uniformity [17]. In granulation and coating processes, infrared energy

promotes uniform solvent evaporation and rapid film formation, leading to improved product quality [16]. Furthermore, IR technology has been explored for microbial decontamination and surface sterilization of pharmaceutical materials, offering an alternative to conventional thermal sterilization methods [18].

5. Ohmic heating (Electrical resistance heating) in pharmaceutical processing

5.1 Principle and working mechanism of ohmic heating: Ohmic heating, also known as electrical resistance heating, is based on the direct passage of alternating electrical current through a conductive material, generating internal heat due to electrical resistance [19]. The heat generated follows Joule's law, where thermal energy is proportional to the square of current, electrical resistance, and processing time. Unlike conventional surface heating methods, ohmic heating produces uniform volumetric heating throughout the material, minimizing temperature gradients and hot spots [20]. This internal heat generation improves process efficiency and reduces overall heating time, making it attractive for temperature-sensitive pharmaceutical materials.

5.2 Advantages of ohmic heating for green pharmaceutical manufacturing: Ohmic heating offers several sustainability advantages, including rapid heating rates, reduced energy consumption, precise temperature control, and minimal thermal degradation of active pharmaceutical ingredients (APIs) [19]. Since heat is generated directly within the material, energy losses associated with heat transfer surfaces are significantly reduced. Additionally, ohmic systems operate without combustion fuels, lowering carbon emissions and supporting green manufacturing principles [20]. The technology also enables continuous processing and scalable production, which is essential for industrial pharmaceutical operations.

5.3 Pharmaceutical applications of ohmic heating: Ohmic heating has been explored for pharmaceutical liquid sterilization, suspension heating, drying enhancement, crystallization control, and bioprocessing applications. In liquid formulations such as syrups and injectable solutions, ohmic heating provides rapid microbial inactivation while preserving product quality [19]. It has also been investigated for controlled crystallization processes, where uniform temperature distribution improves crystal size distribution and polymorphic stability [20]. Furthermore, ohmic-assisted drying and extraction processes demonstrate improved mass transfer efficiency, making the method suitable for herbal and biopharmaceutical product processing.

6. Ultrasound-assisted heating and sonothermal processing in pharmaceutical applications

6.1 Principle of ultrasound-assisted heating (Sonothermal effect): Ultrasound-assisted heating operates through the phenomenon of acoustic cavitation, where high-frequency sound waves (20 kHz–10 MHz) generate microscopic bubbles in liquid media that rapidly collapse, producing localized high temperatures and pressures [10]. This process creates intense micro-mixing, enhanced heat transfer, and localized "hot spots" that accelerate chemical reactions and physical transformations without raising bulk temperatures excessively [4]. Compared to conventional thermal heating, ultrasound promotes rapid energy transfer at the molecular level, enabling efficient and controlled heating with lower energy input, making it suitable for green pharmaceutical processing.

6.2 Green advantages of ultrasound heating in pharmaceutical manufacturing: Ultrasound-assisted heating offers several sustainability benefits, including reduced reaction time, lower solvent consumption, improved mass transfer, and decreased thermal degradation of heat-sensitive drugs [4]. The technology allows reactions and extraction processes to occur at lower bulk temperatures, thereby minimizing energy requirements and carbon footprint. Additionally, ultrasound systems can be integrated with continuous-flow reactors, supporting process intensification and scalable green manufacturing [10]. These features align with green chemistry principles such as energy efficiency, waste minimization, and safer processing conditions.

6.3 Pharmaceutical applications of sonothermal processing: Sonothermal techniques have been widely applied in pharmaceutical synthesis, nanomaterial fabrication, drug crystallization, and herbal extraction. Ultrasound-assisted synthesis enhances reaction yields and purity of pharmaceutical intermediates by improving reactant dispersion and accelerating kinetics [4]. In nanotechnology, ultrasound facilitates uniform nanoparticle formation and drug encapsulation, improving drug delivery performance [10]. Furthermore, ultrasound-assisted extraction has shown superior recovery of bioactive compounds from medicinal plants, reducing solvent use and extraction time while preserving thermolabile constituents.

7. Infrared (IR) heating technology in pharmaceutical processing

7.1 Principle of infrared heating: Infrared heating is based on the direct transfer of electromagnetic radiation in the wavelength range of 0.7–1000 μm to materials, where radiant energy is absorbed and converted into heat at the molecular level [21]. Unlike conventional conduction-based heating, infrared radiation enables rapid and uniform surface

heating with minimal heat loss to the surrounding environment. IR heating enhances molecular vibration and rotational energy, leading to faster moisture removal and controlled thermal processing. The ability to deliver targeted energy makes infrared heating highly efficient for pharmaceutical drying, coating, and thermal treatment processes.

7.2 Green chemistry advantages of infrared heating: Infrared heating significantly reduces energy consumption and processing time compared to conventional ovens and hot-air systems [18]. The technology enables precise temperature control, minimizes thermal gradients, and lowers operational costs. Reduced processing time decreases degradation of heat-sensitive active pharmaceutical ingredients (APIs), improving product quality and stability. Moreover, infrared systems require minimal preheating and generate lower carbon emissions, aligning with green chemistry principles of energy efficiency and environmental sustainability [21].

7.3 Pharmaceutical applications of infrared heating: Infrared heating has been successfully applied in pharmaceutical drying of granules and powders, tablet coating, solvent evaporation, and sterilization processes. Studies have demonstrated improved drying kinetics and uniform moisture removal using IR-assisted drying methods [18]. In coating operations, infrared heating enhances film formation and adhesion while reducing coating defects. Additionally, IR technology is increasingly explored for continuous manufacturing lines, enabling scalable, eco-friendly pharmaceutical production with improved process control.

8. Induction and magnetic heating technologies in pharmaceutical applications

8.1 Principle of induction and magnetic heating: Induction heating operates on the principle of electromagnetic induction, where an alternating magnetic field generates eddy currents within electrically conductive materials, producing rapid and localized heat generation [23]. Magnetic heating, particularly using magnetic nanoparticles, relies on hysteresis loss and Néel/Brownian relaxation mechanisms to convert alternating magnetic field energy into thermal energy [22]. These contactless heating techniques allow precise temperature control and uniform energy distribution, making them highly suitable for controlled pharmaceutical processing and biomedical applications.

8.2 Sustainability and Green Chemistry Benefits: Induction and magnetic heating technologies are considered environmentally sustainable due to high energy efficiency and minimal heat loss to surroundings [23]. These systems provide rapid heating rates, reduced processing times, and lower electricity consumption compared to conventional thermal

methods. The absence of direct flame or heating elements minimizes contamination risks and supports clean manufacturing environments. Furthermore, localized heating reduces thermal degradation of active pharmaceutical ingredients (APIs) and excipients, aligning with green chemistry goals of energy conservation and safer processing conditions [22].

8.3 Pharmaceutical and biomedical applications: In pharmaceutical manufacturing, induction heating is increasingly used for sealing blister packs, sterilizing containers, drying coatings, and activating polymer curing processes [23]. Magnetic heating using iron oxide nanoparticles has gained attention in drug delivery systems, controlled drug release, and hyperthermia-based cancer therapies [22]. These approaches enable targeted thermal activation, improved process reproducibility, and reduced solvent usage. The integration of induction and magnetic heating into continuous manufacturing platforms further enhances scalability, operational efficiency, and environmental sustainability in pharmaceutical production.

9. Ultrasound-assisted heating (Sonochemical heating) in pharmaceutical processing

9.1 Principle and mechanism: Ultrasound-assisted heating is based on acoustic cavitation, where high-frequency sound waves generate microscopic bubbles in liquid media that rapidly grow and collapse, producing localized high temperatures and pressures [10]. This phenomenon enhances mass transfer, accelerates chemical reactions, and improves heat distribution within reaction systems [25]. Unlike conventional heating, sonochemical processes deliver energy directly into the reaction medium, enabling uniform and rapid thermal effects at relatively low bulk temperatures, which is advantageous for temperature-sensitive pharmaceutical compounds.

9.2 Green chemistry advantages: Ultrasound-assisted heating aligns with green chemistry principles by reducing reaction time, lowering solvent consumption, and decreasing energy requirements [24]. The technology promotes milder reaction conditions, minimizes by-product formation, and improves reaction selectivity. Additionally, ultrasound enhances extraction efficiency of bioactive compounds from plant materials using greener solvents such as water and ethanol, supporting sustainable pharmaceutical raw material processing [4].

9.3 Pharmaceutical applications: In pharmaceutical sciences, ultrasound-assisted heating is widely applied in drug extraction, nanoparticle synthesis, crystallization, emulsification, and formulation development [25]. It improves dissolution rates of poorly soluble drugs, enhances encapsulation efficiency in polymeric carriers, and facilitates uniform particle size distribution. Ultrasound is also utilized in sterilization and cleaning of pharmaceutical

equipment due to its strong cavitation-induced decontamination effect. These advantages make sonochemical heating a promising eco-friendly alternative for modern pharmaceutical manufacturing.

10. Infrared heating technology in pharmaceutical applications

10.1 Principle and working mechanism: Infrared (IR) heating operates on the principle of electromagnetic radiation transfer, where energy is delivered directly to materials through radiation rather than convection or conduction [29]. Infrared waves penetrate materials and cause molecular vibration and rotational excitation, resulting in rapid and uniform internal heating [26]. Compared to conventional thermal systems, IR heating provides faster response time, higher energy efficiency, and reduced heat loss, making it suitable for pharmaceutical processes requiring controlled and uniform temperature profiles.

10.2 Green chemistry and energy efficiency advantages: Infrared heating supports green processing by minimizing energy consumption, reducing processing time, and eliminating the need for excessive solvent heating [27]. It offers precise temperature control and selective heating of target materials, thereby preventing thermal degradation of heat-sensitive active pharmaceutical ingredients (APIs). Additionally, IR technology reduces carbon footprint by improving energy utilization efficiency and enabling continuous processing operations, which aligns with sustainable pharmaceutical manufacturing goals.

10.3 Pharmaceutical applications: Infrared heating has been widely applied in drying of granules, powders, and herbal extracts, moisture removal during tablet coating, sterilization of packaging materials, and enhancement of solid-state reactions [28]. In formulation development, IR-assisted drying improves product uniformity and reduces drying time without compromising drug stability. It is also utilized in solvent evaporation processes and quality control studies involving thermal characterization. These applications demonstrate IR heating as an effective eco-friendly alternative to conventional thermal systems in pharmaceutical industries.

11. Ohmic heating technology in pharmaceutical processing

11.1 Principle and heating mechanism: Ohmic heating (also known as Joule heating or electrical resistance heating) is based on the direct conversion of electrical energy into thermal energy when an alternating electric current passes through a conductive material [33]. Heat is generated uniformly within the product matrix according to Ohm’s law, eliminating temperature gradients commonly observed in conventional surface heating methods [32].

This volumetric heating mechanism enables rapid temperature rise, precise control, and homogeneous thermal distribution, making it suitable for pharmaceutical suspensions, gels, liquid formulations, and semi-solid dosage forms.

11.2 Green processing advantages: Ohmic heating is recognized as an environmentally sustainable heating technology due to its high energy efficiency, reduced processing time, and minimal thermal losses [31]. Unlike steam or oil-based heating systems, ohmic heating does not require intermediate heat transfer media, thereby lowering operational energy consumption and carbon emissions. Furthermore, the absence of hot surfaces minimizes fouling and product degradation, supporting clean-label manufacturing and green chemistry principles in pharmaceutical production [32].

11.3 Pharmaceutical applications: In pharmaceutical sciences, ohmic heating has been explored for sterilization of liquid formulations, enhancement of dissolution rates, extraction of bioactive compounds, and controlled heating during granulation and coating processes [30]. It is particularly effective for heat-sensitive herbal extracts and protein-based formulations due to uniform temperature distribution and reduced thermal stress. Additionally, ohmic heating enables continuous processing, which improves scalability and process reproducibility in modern pharmaceutical manufacturing environments.

12. Radio frequency (RF) heating and dielectric heating in pharmaceutical applications

12.1 Principle and heating mechanism: Radio frequency (RF) heating operates within the electromagnetic spectrum range of 1–300 MHz and relies on dielectric polarization and ionic conduction to generate heat within materials [35]. When an alternating electromagnetic field is applied, polar molecules realign rapidly, producing internal friction and volumetric heating. Unlike conventional conduction-based heating, RF heating penetrates deeper into materials, ensuring uniform temperature distribution even in bulk pharmaceutical matrices [36]. This property makes RF heating particularly useful for thick pharmaceutical batches and moisture-rich formulations.

12.2 Sustainability and process efficiency benefits: RF heating offers significant advantages in terms of energy efficiency, reduced processing time, and lower thermal degradation of active pharmaceutical ingredients (APIs) [34]. The ability to selectively heat target materials minimizes unnecessary energy consumption and supports sustainable manufacturing practices. Additionally, RF technology reduces reliance on steam boilers and fossil fuel-based heating systems, thereby decreasing greenhouse gas emissions and operational costs in pharmaceutical facilities.

12.3 Pharmaceutical applications: In pharmaceutical manufacturing, RF heating has been applied for drying of granules, moisture equilibration in powders, sterilization of packaging materials, microbial load reduction, and enhancement of solvent evaporation processes [35]. RF-assisted drying improves product uniformity and preserves thermolabile compounds compared to conventional hot air drying. Furthermore, RF heating is increasingly being explored for scale-up processes due to its compatibility with continuous manufacturing systems and automated process control.

13. Ultrasound-assisted heating and sonothermal processing in pharmaceutical sciences

13.1 Principle and mechanism of action: Ultrasound-assisted heating utilizes high-frequency sound waves (typically 20–100 kHz) to generate localized thermal and mechanical effects through a phenomenon known as acoustic cavitation [10]. Cavitation involves the formation, growth, and collapse of microbubbles in liquid media, producing localized hotspots with extremely high temperature and pressure. These microenvironmental conditions enhance heat transfer, mass transfer, and reaction kinetics, enabling rapid and efficient thermal processing compared to conventional heating techniques [15].

13.2 Environmental and energy efficiency advantages: Ultrasound-based processing aligns with green chemistry principles by reducing reaction times, minimizing solvent usage, and lowering overall energy consumption [24]. The technology allows selective energy delivery to reaction sites, decreasing thermal stress on heat-sensitive pharmaceutical ingredients. Additionally, ultrasound facilitates lower-temperature processing, which preserves drug stability and reduces degradation of thermolabile compounds, contributing to sustainable pharmaceutical manufacturing practices.

13.3 Pharmaceutical applications: In pharmaceutical sciences, ultrasound-assisted heating is widely used for extraction of phytochemicals, enhancement of drug dissolution rates, nanoparticle synthesis, crystallization control, emulsification, and sterilization processes [24]. Sonothermal techniques improve yield and purity of herbal extracts and promote uniform particle size distribution in nanocarrier systems. Ultrasound is also employed in accelerating chemical reactions and improving formulation homogeneity, making it a versatile tool for modern pharmaceutical research and industrial applications.

14. Supercritical fluid heating and processing in pharmaceutical applications

14.1 Principle and operating mechanism: Supercritical fluid (SCF) processing utilizes substances above their critical temperature and pressure, where they exhibit combined

properties of gases and liquids. Supercritical carbon dioxide (SC-CO_2) is the most widely used medium due to its low critical point (31.1°C, 7.38 MPa), non-toxicity, non-flammability, and environmental safety [37]. In the supercritical state, CO_2 exhibits high diffusivity and low viscosity, allowing rapid mass transfer and efficient heat distribution within pharmaceutical matrices [39]. Controlled pressure and temperature adjustments enable selective solvation and precise thermal processing.

14.2 Green chemistry and sustainability benefits: SCF technology aligns strongly with green chemistry principles by minimizing organic solvent usage, reducing waste generation, and enabling solvent-free product recovery [38]. The low operating temperature of SC-CO_2 protects thermolabile drugs from degradation while achieving efficient extraction, sterilization, and particle engineering. Furthermore, CO_2 is recyclable within closed-loop systems, significantly lowering environmental impact and operational costs in pharmaceutical manufacturing.

14.3 Pharmaceutical applications: Supercritical fluid processing has been extensively applied for micronization of APIs, controlled drug encapsulation, purification of bioactive compounds, sterilization of medical materials, and enhancement of drug solubility [40]. SCF-based techniques such as rapid expansion of supercritical solutions (RESS) and supercritical antisolvent (SAS) methods enable precise particle size control and improved bioavailability. These advantages make SCF processing a promising platform for sustainable pharmaceutical formulation development and advanced drug delivery systems.

15. Induction heating technology in pharmaceutical manufacturing

15.1 Working principle and heat generation mechanism: Induction heating is based on electromagnetic induction, where an alternating magnetic field induces eddy currents in electrically conductive materials, generating heat internally through resistive losses [42]. Unlike microwave or RF heating, induction heating does not directly heat non-conductive pharmaceutical materials; instead, it heats metallic reactors, vessels, molds, or tooling surfaces that subsequently transfer heat to formulations through controlled conduction. This indirect but highly controllable heating mechanism enables rapid temperature ramping with excellent spatial accuracy, which is valuable for pharmaceutical processes requiring localized thermal input.

15.2 Pharmaceutical manufacturing relevance: In pharmaceutical production, induction heating is increasingly used in equipment sterilization, hot-melt extrusion barrel heating, coating pan temperature control, and reactor jacket heating during synthesis of active

pharmaceutical ingredients (APIs) [41]. Its fast response time enables precise thermal modulation, reducing risks of overheating sensitive intermediates. Induction-assisted hot-melt extrusion improves polymer melting uniformity and drug dispersion while minimizing residence time, thereby preserving drug stability and content uniformity in solid dispersions.

15.3 Process control and GMP compatibility: A major advantage of induction heating lies in its compatibility with automated temperature control systems and Good Manufacturing Practice (GMP) environments [42]. Since no direct flame or heating element contact is involved, contamination risks are minimized. Closed-system integration supports cleanroom manufacturing and continuous pharmaceutical processing. Additionally, induction systems allow programmable thermal profiles, enabling reproducible batch-to-batch quality and improved process validation.

16. Plasma heating and non-thermal plasma technologies in pharmaceutical processing

16.1 Fundamental mechanism of plasma-based heating: Plasma heating utilizes partially ionized gases composed of electrons, ions, radicals, and excited neutral species that possess high reactive energy states [44]. Unlike conventional thermal systems, plasma generates energy through electrical excitation rather than bulk temperature elevation. In pharmaceutical applications, low-temperature atmospheric plasma is preferred, as it delivers surface-level thermal and chemical effects without raising the core temperature of materials. This unique mechanism enables controlled surface modification, microbial inactivation, and chemical activation without damaging temperature-sensitive pharmaceutical compounds.

16.2 Pharmaceutical manufacturing and sterilization applications: Plasma technology has gained significant attention for sterilization of packaging materials, medical devices, inhalation equipment, and drug delivery components [43]. Plasma-assisted decontamination effectively inactivates bacteria, spores, and viruses by disrupting microbial cell membranes and nucleic acids. Additionally, plasma treatment is used for surface activation of polymers to improve tablet coating adhesion, capsule wettability, and transdermal patch bonding performance. These applications enhance formulation quality without introducing chemical residues.

16.3 Advantages for advanced drug delivery systems: Plasma processing supports development of advanced drug delivery platforms by enabling nanoscale surface functionalization and modification of carrier materials [45]. Plasma-treated nanoparticles demonstrate improved dispersion stability and enhanced drug-loading efficiency. In biomedical applications, plasma-assisted crosslinking and surface grafting improve

biocompatibility of implant coatings and controlled-release matrices. This positions plasma heating as a valuable enabling technology for next-generation pharmaceutical formulations.

17. Hybrid and integrated heating systems in pharmaceutical processing

17.1 Concept of hybrid heating platforms: Hybrid heating systems combine two or more complementary thermal technologies to overcome limitations of individual methods and improve process performance [47]. Instead of relying on a single energy source, integrated systems utilize synergistic mechanisms such as volumetric heating, surface activation, mechanical agitation, and electromagnetic excitation. In pharmaceutical manufacturing, hybrid platforms enable better temperature uniformity, faster process kinetics, and improved control over critical quality attributes (CQAs) such as drug stability, particle size distribution, and content uniformity.

17.2 Microwave–ultrasound and RF–Hot air combinations: Microwave–ultrasound hybrid systems have shown enhanced efficiency in herbal extraction, crystallization, and nanoparticle synthesis by combining volumetric microwave heating with ultrasound-induced cavitation effects [4]. This dual-action approach accelerates mass transfer and improves extraction yield of bioactive compounds without excessive thermal stress.

Similarly, radio frequency–hot air hybrid drying systems are used for pharmaceutical granule drying and moisture equilibration. RF provides deep penetration heating while hot air ensures surface moisture removal, resulting in uniform drying and reduced processing time [48].

17.3 Industrial applications and continuous manufacturing integration: Hybrid heating platforms are increasingly integrated with continuous pharmaceutical manufacturing systems, including hot-melt extrusion, fluidized bed drying, and spray coating operations [46]. Induction-assisted extrusion combined with infrared surface heating improves polymer melting control and coating uniformity. Plasma-assisted UV sterilization systems provide dual decontamination mechanisms for packaging materials. These integrated platforms support Industry 4.0 concepts, enabling real-time monitoring, process analytical technology (PAT) integration, and automated control for consistent product quality. Figure 3 illustrates the integration of microwave-assisted heating with auxiliary energy sources such as ultrasound and infrared radiation in a unified reactor chamber. Controlled energy input enhances heat transfer efficiency, improves reaction kinetics, ensures uniform temperature distribution, and supports higher product yield and quality in pharmaceutical synthesis and formulation processes. Figure 4 depicts the operational layout of an advanced green heating reactor, highlighting key components such as the energy source, reaction vessel, temperature

control unit, and product collection system. The configuration demonstrates precise thermal regulation, reduced energy loss, and improved process sustainability compared to conventional heating methods.

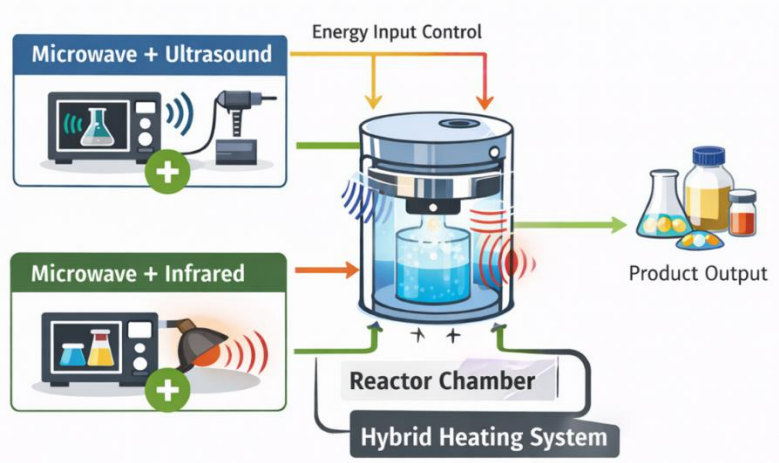

Figure 3. Conceptual framework of hybrid heating systems for pharmaceutical processing.

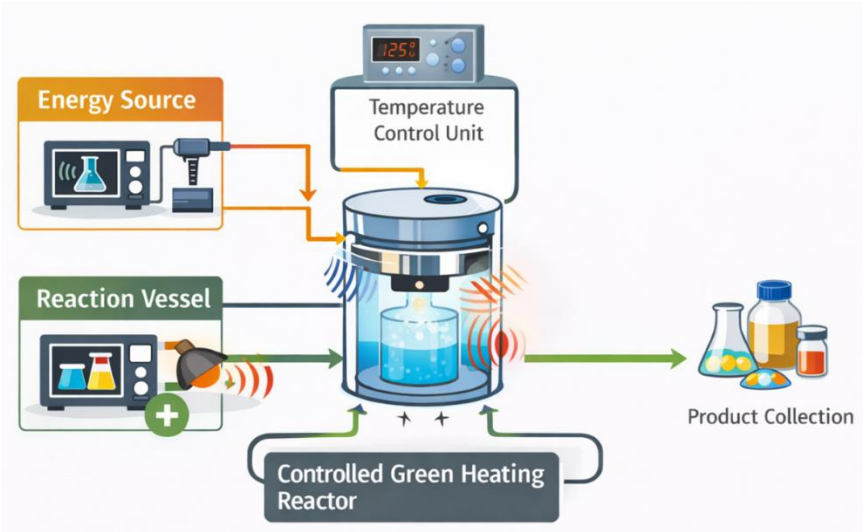

Figure 4. Schematic representation of a controlled green heating reactor setup for pharmaceutical applications.

18. Comparative performance analysis of green heating technologies in pharmaceutical applications

18.1 Evaluation criteria for technology selection: Selection of green heating technologies in pharmaceutical processing requires systematic evaluation based on energy efficiency, temperature uniformity, scalability, process control, product quality impact, and regulatory compatibility [6]. Microwave and radio frequency systems offer volumetric heating and reduced processing time, while infrared and induction heating provide precise surface and

localized thermal control. Ultrasound-assisted heating enhances mass transfer and reaction kinetics but may require auxiliary temperature stabilization systems. Hybrid platforms combine multiple advantages, enabling flexible process optimization depending on formulation type and manufacturing objectives [47].

18.2 Comparative advantages and limitations: Microwave heating demonstrates superior reaction acceleration and solvent reduction but may suffer from non-uniform field distribution in large-scale reactors [7]. Infrared heating offers rapid surface activation and coating uniformity but has limited penetration depth. Induction heating is highly energy-efficient and contamination-free but requires conductive materials. Radio frequency systems provide deeper penetration suitable for bulk drying and granulation but require complex equipment calibration. Hybrid heating systems overcome many individual drawbacks by improving heat homogeneity, reducing batch variability, and enhancing process robustness [4].

18.3 Impact on pharmaceutical product quality: Green heating technologies significantly influence critical quality attributes including crystallinity, dissolution rate, stability, and bioavailability. Controlled microwave-assisted synthesis improves particle size uniformity and polymorphic stability [6]. Infrared-assisted drying minimizes thermal degradation of heat-sensitive drugs. Ultrasound-integrated extraction enhances phytochemical yield while preserving bioactivity. These improvements contribute directly to better therapeutic performance and reduced batch failure risk, supporting quality-by-design (QbD) and continuous manufacturing strategies [46].

19. Regulatory considerations and industrial implementation challenges

19.1 Regulatory acceptance of green heating technologies: Adoption of green heating technologies in pharmaceutical manufacturing must comply with regulatory frameworks such as Good Manufacturing Practices (GMP), International Council for Harmonisation (ICH) guidelines, and Quality by Design (QbD) principles. Regulatory agencies including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) encourage process innovation provided that product quality, safety, and reproducibility are maintained [50]. Continuous manufacturing supported by microwave, infrared, and hybrid heating systems aligns with regulatory initiatives promoting advanced manufacturing technologies and real-time process monitoring [49]. Validation of heating uniformity, temperature control, and batch consistency remains essential for regulatory approval [46].

19.2 Process validation and quality assurance requirements: Implementation of non-conventional heating requires comprehensive validation of critical process parameters such as power input, heating rate, temperature distribution, and residence time. Process Analytical Technology (PAT) tools including near-infrared spectroscopy, thermal imaging, and inline sensors are increasingly used to ensure real-time quality control [52]. Regulatory authorities emphasize risk-based validation strategies to demonstrate reproducibility and robustness of microwave and hybrid systems under commercial manufacturing conditions (ICH Q8, 2009). Proper documentation, equipment qualification (IQ/OQ/PQ), and operator training are mandatory components of regulatory compliance.

19.3 Industrial scale-up challenges: Despite laboratory success, scaling green heating technologies presents engineering and operational challenges. Microwave field non-uniformity, penetration depth limitations, equipment cost, and integration with existing production lines remain significant barriers [6]. Infrared and induction systems require precise material compatibility and thermal calibration for pharmaceutical excipients and packaging materials. Hybrid platforms demand advanced control software and skilled technical personnel. However, advances in reactor design, automation, and digital manufacturing infrastructure are gradually overcoming these limitations and enabling commercial adoption [47].

19.4 Economic and sustainability considerations: Although initial capital investment for green heating equipment is higher than conventional thermal systems, long-term benefits include reduced energy consumption, shorter processing cycles, lower solvent usage, and decreased waste generation. Life cycle assessment studies demonstrate that microwave-assisted and ultrasound-integrated processes significantly reduce carbon footprint and operational costs over extended production cycles [4]. These advantages support pharmaceutical industry goals related to sustainability, regulatory compliance, and corporate environmental responsibility.

20. Future perspectives and research opportunities

20.1 Integration of artificial intelligence and smart process control: Future green heating platforms are expected to incorporate artificial intelligence (AI) and machine learning–based control systems to optimize heating profiles, energy consumption, and product quality. Predictive modeling can enable real-time adjustment of microwave power, ultrasound intensity, and hybrid heating parameters, improving process reproducibility and minimizing thermal degradation of heat-sensitive pharmaceutical compounds [55]. Digital twins and

data-driven optimization strategies will further support continuous manufacturing and personalized formulation development.

20.2 Continuous manufacturing and flow-based green heating: The pharmaceutical industry is transitioning toward continuous manufacturing, where green heating technologies can play a central role. Microwave-assisted flow reactors, infrared tunnel dryers, and hybrid ultrasonic–microwave systems offer precise temperature control and uniform energy distribution in continuous production environments [54]. These systems reduce batch variability, improve scalability, and enhance regulatory compliance through consistent quality output. Future research should focus on modular reactor designs and scalable flow platforms compatible with pharmaceutical-grade materials.

20.3 Development of multi-modal hybrid heating platforms: Emerging research is exploring synergistic combinations of multiple green heating techniques such as microwave–ultrasound, infrared–induction, and microwave–supercritical fluid systems. These integrated platforms enhance mass transfer, reaction kinetics, and thermal efficiency while reducing solvent usage and processing time [4]. Optimization of hybrid architectures offers significant opportunities for pharmaceutical synthesis, crystallization, drying, and extraction processes.

20.4 Sustainability-oriented process innovation: Future pharmaceutical manufacturing will increasingly emphasize carbon neutrality and circular economy principles. Green heating technologies can be combined with renewable energy sources such as solar-assisted infrared systems and electrically powered induction heating supported by green electricity grids [53]. Life cycle assessment–guided process design will help quantify environmental benefits and guide sustainable manufacturing strategies.

21. Challenges, limitations, and knowledge gaps of green heating technologies in pharmaceutical sciences

21.1 Scalability and industrial translation challenges: Despite strong laboratory-level evidence supporting green heating technologies, their large-scale industrial implementation remains limited. Techniques such as microwave and ultrasound heating often face challenges related to non-uniform energy distribution, reactor design complexity, and scale-dependent loss of efficiency. Pharmaceutical manufacturing requires strict control of temperature, homogeneity, and reproducibility, which can be difficult to maintain during scale-up. Furthermore, limited availability of GMP-compliant industrial equipment restricts wider adoption in regulated pharmaceutical environments [6].

21.2 Equipment cost and infrastructure constraints: High initial capital investment for specialized reactors, shielding systems, and process control units represents a significant barrier, particularly for small and medium-scale pharmaceutical manufacturers. Microwave generators, induction coils, and hybrid heating platforms require customized installation and maintenance. In addition, retrofitting existing pharmaceutical plants to accommodate these technologies can be costly and technically challenging, slowing industry-wide transition toward greener heating solutions [53].

21.3 Process control, validation, and reproducibility issues: Achieving precise process control and batch-to-batch reproducibility is critical in pharmaceutical production. Green heating methods may exhibit localized hot spots, uneven electromagnetic field distribution, or cavitation-induced variability, which complicate process validation. Limited availability of standardized protocols and real-time monitoring tools further hampers regulatory acceptance. Robust process analytical technology (PAT) integration is still underdeveloped for many emerging heating systems [55].

21.4 Regulatory acceptance and knowledge gaps: Regulatory uncertainty remains a major challenge, as guidance documents specifically addressing green heating technologies are scarce. Lack of harmonized regulatory frameworks, limited long-term stability data, and insufficient toxicological assessment of process-induced changes create hesitancy among manufacturers. Moreover, comparative life-cycle and environmental impact studies remain limited, highlighting critical knowledge gaps that must be addressed to support evidence-based regulatory decision-making [54].

22. Comparative evaluation of green heating technologies for pharmaceutical applications: This section provides a critical comparison of major green heating technologies used in pharmaceutical research and manufacturing based on energy efficiency, scalability, reaction control, sustainability impact, and industrial feasibility.

Table 2: Performance comparison of heating Technologies. (Source: 6,52,53)

Heating technology	Energy efficiency	Reaction rate enhancement	Scalability	Pharmaceutical compatibility	Sustainability advantage
Microwave heating	Very high	Excellent	Moderate	High (API synthesis, extraction)	Reduced energy consumption
Ultrasound heating	High	High	Moderate	High (extraction, nanoparticle synthesis)	Solvent reduction
Induction	High	Very high	High	Excellent (metal-	Localized

heating				catalyzed reactions)	heating efficiency
Infrared heating	Moderate–High	Moderate	High	Good (drying, crystallization)	Rapid surface heating
Ohmic heating	Very high	High	High	Excellent (bioprocessing, sterilization)	Uniform volumetric heating
Flow reactor heating	High	Excellent	Very high	Excellent (continuous API production)	Reduced waste generation
Solar thermal heating	Moderate	Low–Moderate	Limited	Supplementary processes	Renewable energy integration
Hybrid heating systems	Very high	Excellent	High	Excellent	Process optimization

22.1 Selection criteria for pharmaceutical applications: The selection of heating technology depends on process objectives, regulatory requirements, and product sensitivity. Microwave and ultrasound systems are preferred for laboratory-scale synthesis and extraction due to rapid heating and high reaction efficiency. Induction and ohmic heating demonstrate superior performance for large-scale pharmaceutical production because of precise temperature control and volumetric heating capability. Continuous flow heating offers unmatched scalability and reproducibility, aligning with modern Quality by Design (QbD) principles [55].

Table 3. Pharmaceutical processing applications of emerging green heating technologies.

Process	**Microwave**	**Ultrasound**	**Infrared**	**Ohmic**	**Hybrid systems**	**Reference**
API Synthesis	✓	✓	–	✓	✓	[3,6,58]
Drying	✓	–	✓	–	✓	[28,21,59]
Extraction	✓	✓	–	–	✓	[15,10]
Sterilization	–	–	✓	✓	✓	[30,44]
Crystallization	✓	✓	–	–	✓	[10,6]

✓ = Applicable / Demonstrated, – = Limited application / Not commonly used

22.2 Environmental and economic impact comparison: Green heating technologies significantly reduce solvent consumption, processing time, and energy demand compared to conventional thermal methods. Hybrid systems further improve efficiency by combining strengths of multiple energy sources. However, initial infrastructure cost and equipment complexity remain limiting factors. Long-term operational savings, reduced waste disposal

costs, and lower carbon footprint make these technologies economically viable over time [54].

Table 4. Environmental sustainability assessment of heating technologies used in pharmaceutical processing.

Method	Energy efficiency	Solvent consumption	Carbon footprint impact	Compliance with green chemistry principles	Reference
Conventional heating	Low	High	High	Partial compliance	[1,2]
Microwave heating	High	Reduced	Low	Excellent	[3,6]
Ultrasound heating	High	Reduced	Low	Excellent	[10,15]
Infrared heating	Moderate	Low	Moderate	Good	[21,28]
Ohmic heating	Very High	Minimal	Very Low	Excellent	[30,55]

CONCLUSION AND FUTURE PERSPECTIVES: Green heating technologies have emerged as transformative tools for improving sustainability, efficiency, and process control in pharmaceutical research and manufacturing. Microwave-assisted synthesis, ultrasound irradiation, induction heating, infrared processing, ohmic heating, continuous flow reactors, solar-assisted systems, and hybrid heating platforms collectively demonstrate superior performance over conventional thermal methods by reducing reaction time, solvent consumption, and energy demand while enhancing product yield and reproducibility. These technologies also support regulatory initiatives such as Quality by Design (QbD) and Process Analytical Technology (PAT), enabling real-time monitoring and improved process robustness.

Despite significant advantages, large-scale industrial adoption remains challenged by equipment cost, limited standardization, scale-up complexity, and regulatory validation requirements. Future research should focus on developing integrated hybrid platforms, AI-assisted temperature control systems, energy-efficient reactor designs, and modular continuous manufacturing units. Greater collaboration between academia, pharmaceutical industries, and regulatory agencies will be essential to accelerate translation from laboratory-scale innovation to commercial production. The adoption of renewable energy-assisted heating and smart automation is expected to further strengthen the environmental

sustainability of pharmaceutical manufacturing, positioning green heating technologies as central components of next-generation drug production systems.

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