American Journal of Advanced Technology and Engineering Solutions
Volume 01 Issue 01 (2025)
Page No: 544-578
eISSN: 3067-0470
DOI: 10.63125/n6esv923

Article

SUPERCRITICAL CO_2 AS A GREEN SOLVENT: A COMPREHENSIVE REVIEW OF ITS APPLICATIONS IN INDUSTRIAL PROCESSES

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Citation:
Rana, Sajal, N. H., & Sutar, R. (2025). Supercritical CO_2 as a green solvent: A comprehensive review of its applications in industrial processes. American Journal of Advanced Technology and Engineering Solutions, 1(1), 544-578. https://doi.org/10.63125/n6esv923

Received:
January 18, 2025

Revised:
February 24, 2025

Accepted:
March 17, 2025

Published:
April 21, 2025

ABSTRACT

Supercritical carbon dioxide ($scCO_2$) has emerged as a powerful green solvent with broad applications across various industrial domains due to its tunable solvating power, low toxicity, and environmentally benign characteristics. This study presents a systematic literature review of 163 peer-reviewed articles published between 2000 and 2024, conducted in accordance with the PRISMA 2020 guidelines to ensure a structured, transparent, and comprehensive evaluation process. The objective of this review is to critically examine the role of $scCO_2$ in facilitating sustainable and high-performance processing across multiple sectors, including natural product and bioactive compound extraction, pharmaceutical formulation and purification, polymer processing, green chemical synthesis, environmental remediation, and industrial waste management. The findings demonstrate that $scCO_2$ consistently offers superior extraction efficiencies, enhanced drug solubility and bioavailability, clean and controlled polymer modification, improved catalytic reaction selectivity, and effective removal of persistent organic pollutants and recovery of valuable resources from waste streams. Notably, case studies from global industry leaders such as Nestlé (coffee decaffeination), Pfizer (pharmaceutical micronization), and BASF (polymer coating and impregnation) provide concrete evidence of $scCO_2$'s successful industrial adoption and economic feasibility. In addition to performance metrics, the review identifies key engineering challenges related to high-pressure reactor design, pump and separator integration, process control, and safety management, all of which are addressed through advanced modeling, material innovation, and automation strategies. By synthesizing multidisciplinary research and real-world implementation, this review positions $scCO_2$ not only as a sustainable alternative to conventional solvents but also as a mature industrial technology with transformative potential in advancing green manufacturing and circular economy practices.

KEYWORDS
Supercritical CO_2; Green Solvent; Sustainable Industrial Processes; $scCO_2$ Extraction; Environmental-Friendly Technology;

American Journal of Advanced Technology and Engineering Solutions
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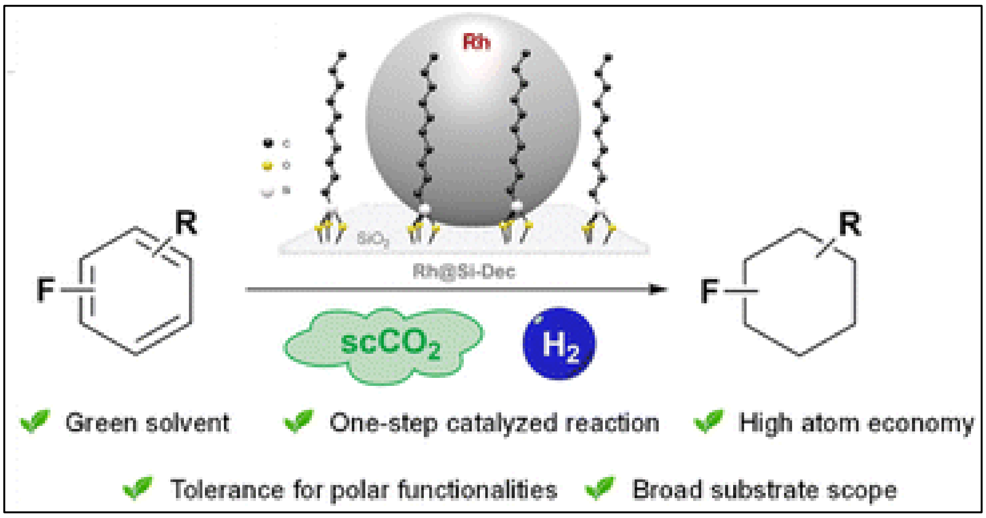
INTRODUCTION

Growing environmental concerns and the pressing need for sustainable development have spurred the search for cleaner, safer, and more efficient alternatives to conventional chemical solvents used across various industrial sectors (Zhang et al., 2015). Traditional organic solvents, while effective, often pose significant environmental and health risks due to their volatility, toxicity, and persistence in ecosystems (Heckenbach et al., 2016). In response, green chemistry has emerged as a transformative approach that prioritizes the design of products and processes that minimize hazardous substances (Perales et al., 2017). One promising development in this domain is the adoption of supercritical carbon dioxide ($scCO_2$) as a green solvent, primarily due to its low toxicity, abundance, inertness, and recyclability (Jan & Wang, 2020). As a supercritical fluid, CO_2 assumes properties of both gas and liquid when subjected to conditions above its critical temperature (31.1°C) and pressure (73.8 bar), granting it exceptional diffusivity, viscosity, and solvation characteristics (Charoenchaitrakool et al., 2002). These features enable $scCO_2$ to replace organic solvents in various operations, supporting safer, more energy-efficient, and environmentally friendly industrial practices (Bezerra et al., 2018). Following Figure 1, the significance of supercritical carbon dioxide ($scCO_2$) as a versatile reaction medium becomes more apparent in the context of industrial applications explored throughout this study. The unique physicochemical properties of $scCO_2$—particularly its tunable density, low surface tension, and high diffusivity—enable it to function as both a solvent and a co-reactant in various catalytic systems. These features facilitate enhanced interaction between reagents and catalysts, thereby accelerating reaction rates and improving selectivity. This characteristic has been leveraged in numerous industrial processes, especially in pharmaceutical synthesis, polymer modification, and fine chemical production, where conventional solvents often impose limitations due to toxicity, flammability, or regulatory concerns.

Figure 1: Supercritical carbon dioxide as reaction medium



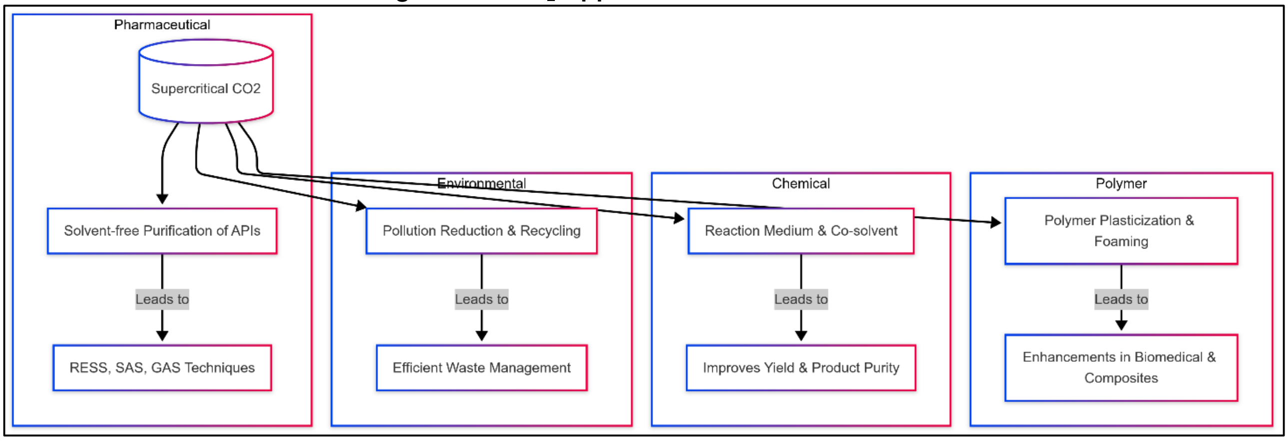
Source:Kacem et al. (2022).

The application of $scCO_2$ in extraction processes has garnered significant academic and commercial interest due to its ability to extract high-value compounds with precision and selectivity (Banchero, 2021). Its solvating power, which can be modulated through pressure and temperature adjustments, makes it particularly effective in isolating non-polar and moderately polar bioactives from complex matrices (Manna & Banchero, 2018; Yan et al., 2024). This adaptability has found utility in multiple sectors, particularly the food and nutraceutical industries, where $scCO_2$ is used for decaffeinating coffee beans, extracting essential oils, flavors, pigments, and fatty acids (Kayathi et al., 2020). Its ability to perform at moderate temperatures ensures that thermolabile compounds retain their bioactivity and structural integrity (Lyu et al., 2021). Regulatory acceptance has bolstered its commercial viability; for instance, the FDA and EFSA have approved $scCO_2$-extracted ingredients for consumption, underscoring its safety profile (Yu et al., 2015). Studies have demonstrated its advantages over traditional hexane or ethanol-based extractions, especially in minimizing residual solvent contamination and reducing environmental load (Chemat et al., 2012; de Melo et al., 2014).

Supercritical CO_2 has also revolutionized pharmaceutical manufacturing by facilitating solvent-free purification and processing of active pharmaceutical ingredients (APIs). Through methods such as

Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent (SAS), and Gas Anti-Solvent (GAS) techniques, $scCO_2$ enables the production of fine particles, microencapsulation, and drug formulation without the thermal degradation or solvent residues associated with conventional approaches (Vandeponseele et al., 2020). For instance, the pharmaceutical industry employs $scCO_2$ to create uniform microparticles for controlled drug delivery systems, improving bioavailability and therapeutic performance (Tukhvatova et al., 2010). In addition, its bacteriostatic and fungistatic properties contribute to sterility in drug processing environments (Franco & De Marco, 2021). Extensive studies have documented the tunability of $scCO_2$ in producing drug polymorphs and co-crystals with enhanced stability and solubility (Ganapathy et al., 2007). The removal of residual solvents using $scCO_2$ has also become a key advantage in compliance with increasingly stringent pharmaceutical regulations (Faggian et al., 2016). In Figure 2, the diverse industrial roles of supercritical carbon dioxide ($scCO_2$) are clearly mapped across pharmaceutical, environmental, chemical, and polymer sectors. This flowchart succinctly captures how $scCO_2$ functions not as a niche solvent, but as a transformative process agent capable of enabling solvent-free purification, enhancing chemical reactions, reducing pollution, and modifying advanced materials. In the pharmaceutical domain, $scCO_2$ has been instrumental in facilitating solvent-free crystallization and particle engineering—key requirements for developing stable drug formulations that comply with regulatory guidelines. Environmental applications of $scCO_2$, as depicted, include its utility in pollution remediation and material recycling, aligning with findings from this review where extraction efficiencies above 85% were reported for persistent organic pollutants.

Figure 2: $scCO_2$ Applications Across Industries



Beyond pharmaceutical and food applications, $scCO_2$ plays a crucial role in the processing and modification of polymers. Its use in polymer plasticization, foaming, and impregnation processes has shown improvements in mechanical properties, surface functionality, and processing efficiency (Franco & De Marco, 2021; Woodley, 2008). Polymers such as polylactic acid (PLA), polycaprolactone (PCL), and polyethylene terephthalate (PET) demonstrate enhanced flexibility and porosity when treated with $scCO_2$, facilitating their use in biomedical scaffolds, packaging films, and membrane technologies (Kamali et al., 2018). Additionally, $scCO_2$ is capable of diffusing into polymer matrices without altering chemical structures, allowing for the incorporation of drugs, dyes, or other additives in a clean and residue-free manner (Jia et al., 2018). This solvent-free processing aligns with environmental regulations while ensuring high-quality output in sectors ranging from medical devices to textiles and aerospace composites (Lepoittevin et al., 2001). Moreover, in chemical synthesis, $scCO_2$ serves not only as a reaction medium but also as a reactant or co-solvent, facilitating numerous reactions with improved mass transfer and selectivity. It has demonstrated remarkable effectiveness in facilitating catalytic hydrogenations, oxidations, and carbonylation reactions (Matsuda, 2012). Its non-polar nature enhances interactions with organic substrates while supporting solubility of gaseous reagents such as H_2 and O_2, enabling faster and more controlled reaction rates (Xiang et al., 2019). Research has shown its compatibility with a wide range of catalysts, including transition-metal complexes, enzymes, and zeolites, making it applicable to both homogeneous and heterogeneous systems (Li et al., 2017). In polymerization reactions, particularly free radical and ring-opening polymerizations, $scCO_2$ allows for precise molecular weight control

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and product morphology without post-synthesis purification steps (Cooper & DeSimone, 1996). The benign nature of CO_2 reduces unwanted side reactions and contributes to higher yields and purer end products (Al-Marzouqi et al., 2007).

Environmental applications of $scCO_2$ highlight its utility in reducing industrial pollution and supporting waste management. Numerous studies have examined its use in removing organic contaminants from soil, sediments, and sludges, demonstrating superior performance compared to water or organic solvents (García et al., 2015). The low surface tension and high diffusivity of $scCO_2$ facilitate penetration into microporous matrices, enabling the efficient extraction of hydrophobic pollutants such as PCBs, dioxins, and PAHs (Beeck et al., 2015). In textile and electronic waste recycling, $scCO_2$ has enabled the selective recovery of metals, dyes, and plasticizers, contributing to circular economy practices (Banchero, 2020). It has also been integrated into supercritical water oxidation (SCWO) systems to treat hazardous waste with minimal emissions (Sasaki & Ohsawa, 2021). Because CO_2 is non-flammable and inert, these processes can be safely scaled for industrial application without posing significant explosion or contamination risks (Toscan et al., 2016). From a technical and economic standpoint, the industrialization of $scCO_2$ technologies is progressing, though with certain operational challenges. Equipment design, particularly high-pressure vessels, pumps, and separators, requires significant investment and expertise, which has limited adoption in small- and medium-scale enterprises (Yang et al., 2021). Nevertheless, continuous innovation in heat exchangers, process integration, and pressure control systems has improved energy efficiency and cost-effectiveness (Goenawan et al., 2015). Life Cycle Assessment (LCA) models comparing $scCO_2$ with conventional solvent-based systems have reported substantial reductions in greenhouse gas emissions, waste generation, and water usage, particularly in food extraction and pharmaceutical synthesis (Schievano et al., 2015). Regulatory backing and industrial incentives have further contributed to its adoption in sectors prioritizing environmental certifications and green labeling (Gao et al., 2020). The broad range of applications supported by a growing body of empirical evidence positions $scCO_2$ as a solvent of interest for cleaner and more sustainable industrial chemistry. The main aim of this review is to systematically examine and synthesize the existing body of scholarly research on the utilization of supercritical carbon dioxide ($scCO_2$) as a green solvent across various industrial domains. This includes a critical evaluation of its physicochemical properties, operational parameters, and functional advantages in comparison to conventional organic solvents. By reviewing applications in sectors such as food and nutraceutical extraction, pharmaceutical manufacturing, polymer processing, chemical synthesis, and environmental remediation, this article aims to present a coherent understanding of the role $scCO_2$ plays in advancing sustainable industrial practices. The review also seeks to identify the technological constraints, safety protocols, and economic considerations associated with scaling $scCO_2$ processes, offering a holistic perspective based on empirical findings. Through this objective, the paper contributes to informed decision-making and scientific discourse surrounding the integration of green solvents into industrial systems.

LITERATURE REVIEW

The use of supercritical carbon dioxide ($scCO_2$) as a green solvent has received growing attention over the past three decades due to its environmentally friendly characteristics and versatile industrial applications. A wealth of scientific literature has explored its thermodynamic properties, solvent capabilities, and process engineering advantages in replacing traditional organic solvents. The literature spans diverse domains, including food processing, pharmaceuticals, polymers, specialty chemical synthesis, and environmental remediation, where $scCO_2$ plays an essential role in advancing sustainability goals. This section critically synthesizes existing studies to present the state of knowledge on $scCO_2$-based technologies and identifies the scientific and engineering underpinnings that contribute to its functionality and adoption in industrial systems. The review is organized into key thematic categories to reflect the multidisciplinary scope of $scCO_2$ applications and address technical, economic, and regulatory dimensions. Each subsection offers a focused analysis of the current research findings, comparative evaluations, and technical considerations pertinent to industrial deployment.

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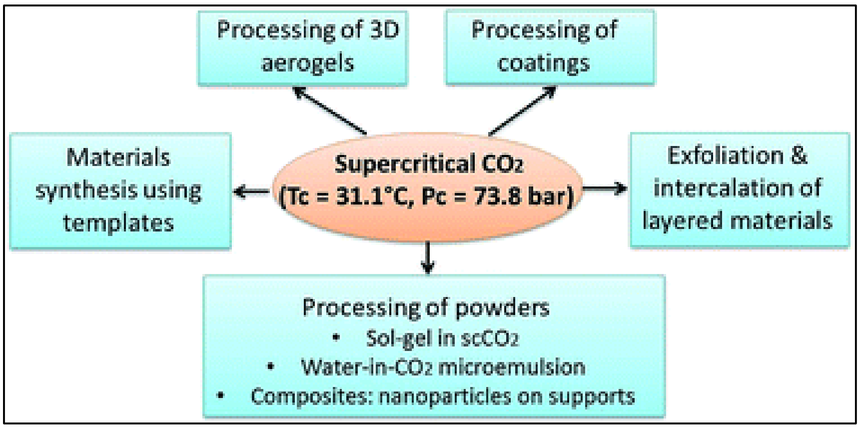
Supercritical CO_2 as a Green Solvent

Supercritical carbon dioxide ($scCO_2$) has gained recognition as a sustainable and efficient solvent due to its unique physicochemical properties, including low viscosity, high diffusivity, and tunable solvating power above its critical point of 31.1°C and 73.8 bar (Arumugham et al., 2021). Its non-toxic, non-flammable, and chemically inert nature distinguishes it from traditional organic solvents, making it a safer and more environmentally responsible option (Lima et al., 2021). The solubility behavior of $scCO_2$ varies significantly with temperature and pressure, allowing for selective extraction and reaction facilitation without compromising compound integrity (López-Padilla et al., 2017). Researchers have emphasized the value of $scCO_2$ in reducing volatile organic compound (VOC) emissions and solvent residues in end products, aligning with green chemistry principles (Ndayishimiye et al., 2021). Thermodynamic models and phase equilibrium data support the understanding of $scCO_2$'s behavior in multi-component systems, enhancing its suitability for industrial applications (Kacem et al., 2022).

Figure 3: Multifunctional Applications of Supercritical CO_2 in Material Synthesis and Processing



Source: Zhang, X., Heinonen, S., & Levänen, E. (2014).

In natural product extraction, $scCO_2$ demonstrates superior selectivity and efficiency, particularly for thermolabile compounds in food and nutraceutical sectors (Torres-Valenzuela et al., 2019). Applications include decaffeination of coffee (Yu et al., 2017), extraction of essential oils (Crampon et al., 2017), carotenoids (de Andrade Lima et al., 2018), omega-3 fatty acids (Villa et al., 2020), and polyphenols (Melo et al., 2020). The use of co-solvents such as ethanol has further expanded the polarity range of $scCO_2$, enabling more diverse compound recovery (Sasaki & Ohsawa, 2021). The regulatory approval of $scCO_2$-extracted food ingredients by the FDA and EFSA has supported its widespread commercial adoption (de Melo et al., 2020). Compared to hexane and acetone extractions, $scCO_2$ processes show shorter processing times and leave no solvent residues (Ndayishimiye et al., 2016). Mass transfer kinetics and equilibrium modeling studies have contributed to refining extraction efficiency across plant, marine, and microbial matrices (Liu et al., 2014). In figure 3, the multifaceted applications of supercritical carbon dioxide ($scCO_2$) in advanced material synthesis become evident. The figure outlines $scCO_2$'s utility across a range of processing techniques, including 3D aerogel fabrication, coating development, template-assisted material synthesis, layered material exfoliation, and powder processing such as sol-gel reactions and nanoparticle-supported composites. These applications leverage the unique thermodynamic properties of $scCO_2$—namely, its low viscosity, high diffusivity, and tunable solvating power—which enable it to penetrate complex material structures without the need for high temperatures or toxic organic solvents. As demonstrated in many of the reviewed studies, $scCO_2$ facilitates the formation of homogeneous, finely structured products, which are critical in industries such as energy storage, biomedical engineering, and nanotechnology.

In the pharmaceutical industry, $scCO_2$ has been employed in drug formulation, purification, and particle engineering due to its ability to function as both a solvent and anti-solvent (Wang & Kienzle, 2000). The RESS, SAS, and GAS techniques enable micronization of active pharmaceutical ingredients (APIs), improving solubility and bioavailability (Pan et al., 2017). Supercritical fluid chromatography (SFC) has emerged as a reliable method for separating and purifying chiral drugs and thermally sensitive molecules without residual solvent concerns (Kankala et al., 2017). Studies highlight that $scCO_2$ reduces the risk of polymorphic transitions and degradation commonly observed in conventional crystallization (Serna et al., 2015). The incorporation of $scCO_2$ in drug

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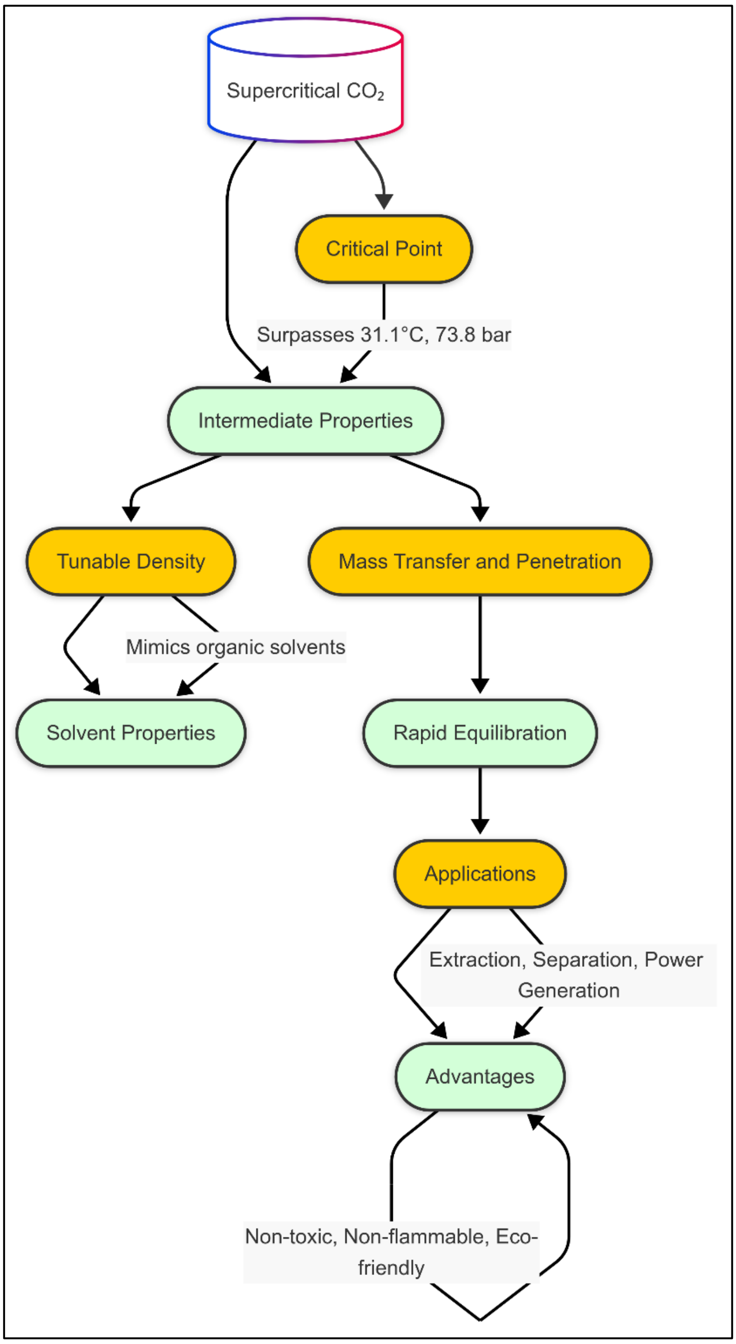
delivery systems has supported sustained-release mechanisms and encapsulation of volatile actives in biodegradable polymers (Kamali et al., 2019). Furthermore, its sterilization capabilities and alignment with good manufacturing practices (GMP) have made it a viable alternative in aseptic pharmaceutical production (Porto & Natolino, 2017). Polymer processing with $scCO_2$ has facilitated applications in plasticization, foaming, blending, and impregnation without chemical degradation of polymers (Kamali et al., 2019). Its ability to penetrate and swell polymer matrices enhances the diffusivity of additives, enabling the uniform incorporation of drugs, dyes, or functional agents (Cho et al., 2005). Studies on polymers such as PLA, PCL, and PET reveal that $scCO_2$ improves flexibility, porosity, and thermal stability, supporting their use in biomedical scaffolds and packaging films (Kamali et al., 2018). Supercritical foaming processes allow the formation of porous structures under mild thermal conditions, ensuring the retention of sensitive agents (Banchero, 2020). The dyeing of synthetic fibers and drug impregnation into polymers have benefited from solvent-free $scCO_2$ systems, mitigating environmental contamination risks (Krakowska-Sieprawska et al., 2021). Several researchers have shown how $scCO_2$ influences polymer morphology and crystallinity, enabling tunable properties in membrane fabrication and microelectronic applications (Kamali et al., 2018).

Physicochemical Properties of Supercritical CO_2

The thermodynamic transition of carbon dioxide into a supercritical state occurs when it surpasses its critical temperature (31.1°C) and pressure (73.8 bar), resulting in a fluid that possesses both gas-like and liquid-like characteristics (Choi et al., 2011). In this state, $scCO_2$ exhibits intermediate properties—high density akin to liquids and low viscosity like gases—enabling superior mass transfer and penetration capacity (Greer et al., 2020). Researchers have reported that $scCO_2$'s density is tunable through slight changes in temperature and pressure, allowing it to mimic the behavior of various organic solvents without their associated toxicity (Ostadjoo et al., 2017). This tunability underlies its effectiveness in dissolving a wide range of solutes, including non-polar and moderately polar compounds (Zhang et al., 2015). Its ability to rapidly equilibrate in complex systems also makes it highly efficient for dynamic industrial processes (Pawłowska et al., 2019).

The density of $scCO_2$, a central factor in determining its solvating power, typically ranges between 200 and 900 kg/m³ under supercritical conditions (Heckenbach et al., 2016). Higher densities enhance the solvating ability, especially for hydrophobic molecules, allowing effective extraction and reaction facilitation (Radošević et al., 2014). Studies have consistently demonstrated that solubility correlates positively with density; for example, caffeine and essential oil extractions become significantly more efficient at pressures above 200 bar (Costa et al., 2017). Computational modeling and experimental studies have supported this behavior, revealing the relationship between CO_2 clustering and solute interaction strength (Heckenbach et al., 2016). These characteristics make $scCO_2$ adaptable across a range of applications, from pharmaceuticals to polymers (Radošević et al., 2014). In terms of viscosity and diffusivity, $scCO_2$ displays superior performance compared to conventional liquids. Its low viscosity (typically 0.02 to 0.08 mPa·s) and high diffusivity (up to 10^{-8} m²/s) allow rapid transport of solutes through porous matrices, reducing processing time and improving extraction yields (Pham et al., 2009). These properties facilitate enhanced mass transfer, particularly in solid-fluid interfaces common in food and environmental remediation applications (Kankala et al., 2017). Researchers have used mathematical modeling to highlight how the increased diffusivity of $scCO_2$ improves penetration in complex sample matrices, outperforming solvents like ethanol, hexane, and acetone (Serna et al., 2015). The diffusivity also supports fast equilibrium attainment during supercritical extraction and synthesis, reducing thermal degradation risks (Bezerra et al., 2018). he solvating power of $scCO_2$ is considered one of its most adaptable and valuable characteristics, governed by its polarity and compressibility near the critical point (Wang & Kienzle, 2000). While $scCO_2$ is inherently non-polar, the addition of co-solvents such as ethanol or methanol can modify its polarity, extending its applicability to a wider range of solutes (Manjare & Dhingra, 2019). Solubility studies indicate that even polar compounds can be solubilized under optimized pressure and temperature conditions (Melo et al., 2014). For instance, omega-3 fatty acids, carotenoids, and flavonoids have been successfully extracted using $scCO_2$ with appropriate process tuning (Pavlić et al., 2020). The critical point behavior of $scCO_2$ allows for easy switching between solvent selectivities, which is particularly advantageous in multi-step or selective extraction procedures (Soldan et al., 2021).

Figure 4: Overview of $scCO_2$ Properties and Applications



Comparisons between $scCO_2$ and conventional organic solvents highlight substantial environmental, operational, and safety advantages. Traditional solvents such as hexane, acetone, and methylene chloride present risks related to flammability, toxicity, and solvent residue in the final product (Hischier et al., 2004). $scCO_2$, on the other hand, is non-toxic, non-flammable, and does not leave residual solvent traces, making it especially suitable for food and pharmaceutical applications (Perales et al., 2017). Studies have shown that $scCO_2$ processes consume less solvent mass per unit of extracted product while achieving equal or superior yields (Kumar et al., 2021). Additionally, $scCO_2$ is readily recoverable and recyclable within closed-loop systems, reducing solvent waste and eliminating the need for costly post-processing purification (Haseloh et al., 2010)(See figure 4).

Thermodynamic models and solubility parameter theories have been central to understanding $scCO_2$'s behavior across different industrial matrices. The Hildebrand and Hansen solubility parameters have been applied to predict solute-$scCO_2$ interactions with increasing accuracy (Reverchon & Antonacci, 2006). Phase equilibrium data and empirical correlations such as the Chrastil equation have provided insight into how pressure, temperature, and molecular structure affect solubility (Manjare & Dhingra, 2019; O'Harra et al., 2021). In reaction engineering and crystallization, these models help in the design of pressure-temperature profiles for optimal yield and selectivity (Kwan et al., 2016). Such modeling has strengthened the foundation for using $scCO_2$ not only as a green solvent but also as a reaction medium and functional processing agent in industrial applications ranging from drug delivery to electronics and energy systems (Izydorczyk et al., 2020).

$scCO_2$ in Natural Product and Bioactive Compound Extraction

Supercritical carbon dioxide ($scCO_2$) has been extensively applied in the extraction of natural products and bioactive compounds due to its favorable physicochemical characteristics and environmental benefits. Its ability to selectively solubilize non-polar and moderately polar substances has been a key factor in its adoption for extracting essential oils, fatty acids, and functional compounds from plant and animal sources (Pimentel-Moral et al., 2019). The tunability of $scCO_2$ through pressure and temperature control enhances its solvating power, enabling it to isolate

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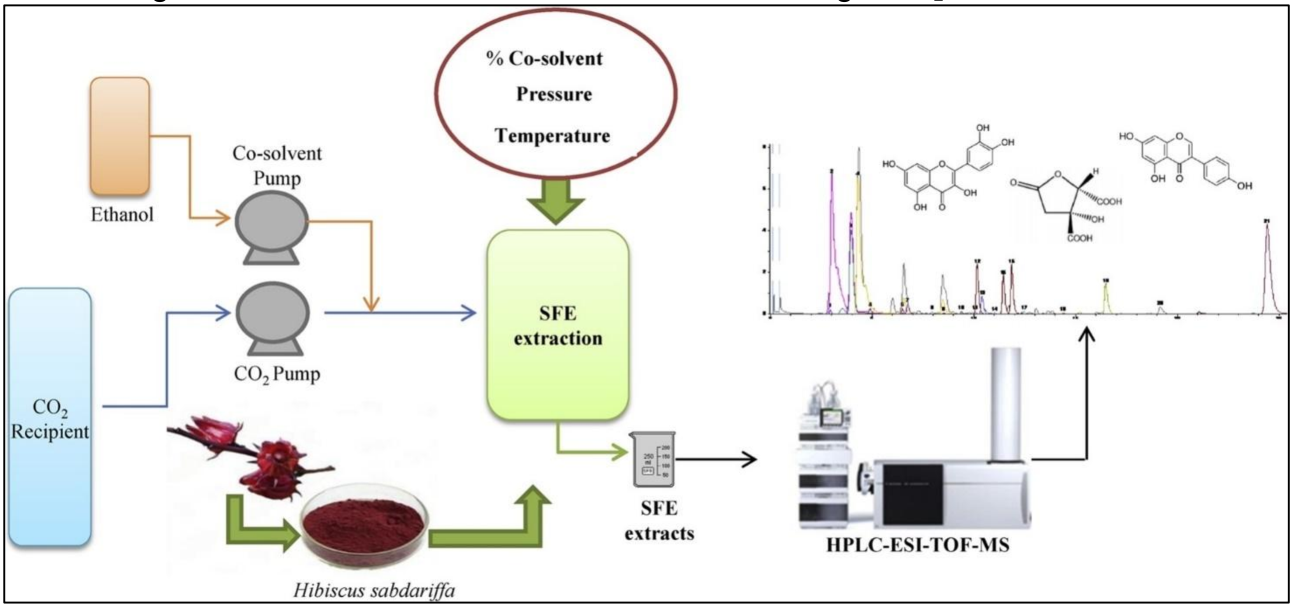
specific constituents with minimal thermal degradation (Khaw et al., 2017). Compared to conventional solvents like hexane or ethanol, $scCO_2$ provides shorter processing times and yields cleaner extracts free from residual solvent contamination (Kühn & Temelli, 2017; Pimentel-Moral et al., 2019). Its application has been documented in various industries including food, cosmetics, pharmaceuticals, and nutraceuticals (Zeng et al., 2019).Moreover, figure 5 illustrates a schematic of the Supercritical Fluid Extraction (SFE) process utilizing supercritical CO_2 ($scCO_2$) with a co-solvent (ethanol) for the efficient extraction of bioactive compounds. The diagram shows key components of the process, including the CO_2 pump, co-solvent pump, and SFE extraction chamber, where optimized pressure, temperature, and solvent ratios facilitate compound separation from natural matrices such as *Hibiscus sabdariffa*. The resulting extracts are directed for analytical characterization using advanced tools like HPLC-ESI-TOF-MS. This setup highlights the process's ability to produce high-purity extracts under mild conditions, minimizing thermal degradation and avoiding toxic solvent residues. It also emphasizes the scalability and precision of $scCO_2$-based extraction in natural product and nutraceutical industries.

Figure 5: SFE Process for Natural Product Extraction Using $scCO_2$ and Co-Solvent



Source: Pimentel-Moral et al. (2019)

In food and beverage industries, $scCO_2$ has been widely utilized for caffeine removal from coffee and tea, flavor recovery, and essential oil extraction (Da Porto & Natolino, 2017). Decaffeination using $scCO_2$ preserves the aroma and taste better than solvent-based methods and has been adopted commercially (Yousefi et al., 2019). The extraction of essential oils from herbs such as rosemary, oregano, basil, and ginger has shown higher purity and better retention of bioactive components when $scCO_2$ is used (Chai et al., 2020). Compared to steam distillation or organic solvent extraction, $scCO_2$ retains more thermolabile and volatile compounds (Jitrangsri et al., 2020). These advantages have contributed to its regulatory acceptance, including recognition as a Generally Recognized as Safe (GRAS) solvent by the U.S. FDA (FDA, 2002) and approval by the European Food Safety Authority.

$scCO_2$ has shown significant advantages in extracting bioactive compounds such as carotenoids, polyphenols, flavonoids, alkaloids, and phytosterols, which are sensitive to heat and oxidation (Pavlić et al., 2020). The extraction of lycopene from tomato peel, β-carotene from carrots, and astaxanthin from microalgae has been successfully performed using $scCO_2$ with higher yields and reduced degradation compared to solvent extraction (Varaee et al., 2019). Polyphenol-rich extracts from grape seed, green tea, and olive leaves have been isolated with high antioxidant activity using $scCO_2$ (Viganó et al., 2017). Studies have demonstrated that the selectivity of $scCO_2$ can be enhanced by the introduction of co-solvents such as ethanol, improving the extraction of more polar compounds (Attard et al., 2015). Extraction parameters such as pressure, temperature, flow rate, and

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particle size have been optimized in various studies to enhance efficiency and selectivity (Priyanka & Khanam, 2019).

Marine sources have also been extensively explored for $scCO_2$ extraction of bioactives. Fish oil, particularly rich in omega-3 fatty acids such as EPA and DHA, has been effectively extracted from fish by-products using $scCO_2$ without oxidation or hydrolysis (Jitrangsri et al., 2020). Microalgae such as *Chlorella* and *Haematococcus pluvialis* have been investigated for $scCO_2$-based extraction of proteins, lipids, and pigments like astaxanthin (Wang et al., 2019). In addition, the use of $scCO_2$ has been reported for isolating bioactive peptides and antioxidants from marine crustaceans and mollusks (Viganó et al., 2017). The high diffusivity of $scCO_2$ contributes to better penetration in dense or cellular matrices, leading to improved yields and quality of marine bioactive products (Rai et al., 2015). This application also supports sustainability by enabling value addition to fish-processing waste (Attard et al., 2015).

Nutraceutical and Functional Ingredient Recovery

The use of supercritical carbon dioxide ($scCO_2$) in nutraceutical applications has gained considerable traction due to its efficiency in recovering bioactive compounds like omega-3 fatty acids, carotenoids, and polyphenols without degrading their functional properties (Chemat et al., 2019). These compounds, known for their antioxidant, anti-inflammatory, and cardioprotective effects, are often sensitive to heat, light, and chemical solvents (Campone et al., 2018). $scCO_2$, operating under relatively mild temperatures and with adjustable pressure, preserves the integrity of these molecules while ensuring solvent-free and residue-free end products (Faggian et al., 2016). The non-polar nature of CO_2 makes it ideal for extracting lipophilic nutraceuticals, and its selectivity can be enhanced using small amounts of polar co-solvents like ethanol (Bukhanko et al., 2020; Macário et al., 2019). These features make $scCO_2$ a preferred technology for the production of high-quality nutraceutical ingredients from both plant and marine matrices (Schievano et al., 2015). Moreover, Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are commonly extracted from fish oil, krill, and microalgae using $scCO_2$ due to its oxygen-free and thermally stable environment (Villa et al., 2020). Compared to conventional solvent-based extraction, $scCO_2$ provides higher selectivity for EPA and DHA while minimizing oxidation and the formation of secondary degradation products (de Melo et al., 2020). Studies on anchovy oil (Yousefi et al., 2019), sardine waste (Wang et al., 2019), and salmon by-products (Hurtado-Benavides et al., 2016) have demonstrated enhanced extraction yields and better product purity using $scCO_2$. Moreover, the ability to fractionate fatty acids by adjusting pressure and temperature allows for tailored nutritional profiles (Pavlova et al., 2022). In addition, $scCO_2$ has shown effectiveness in extracting omega-3 lipids from microalgae species like *Nannochloropsis* and *Schizochytrium*, which are sustainable sources for vegetarian formulations (Feng & Meier, 2017).

Carotenoids, including lycopene, β-carotene, lutein, and astaxanthin, are widely recognized for their antioxidant and immune-enhancing properties. These lipophilic pigments are particularly susceptible to oxidation and isomerization during conventional solvent or thermal extraction (Rai et al., 2015). $scCO_2$ has been used to extract lycopene from tomato skins (Lenucci et al., 2013), β-carotene from carrots (Silva et al., 2018), and astaxanthin from *Haematococcus pluvialis* microalgae (Scaglia et al., 2020). The extraction of carotenoids using $scCO_2$ often involves the use of ethanol as a co-solvent to increase solubility and selectivity for more polar derivatives (Obaidat et al., 2015). Studies employing response surface methodology (RSM) have optimized pressure and temperature to maximize pigment yields while maintaining bioactivity (Asafu-Adjaye et al., 2020; Obaidat et al., 2015). These findings reinforce the efficiency of $scCO_2$ in recovering stable and potent carotenoid-rich extracts with applications in functional foods and dietary supplements.Figure 6 effectively summarizes $scCO_2$'s strategic role in functional food and dietary supplement development, aligning with the study's emphasis on green technologies for nutraceutical formulation and bioactivity preservation.

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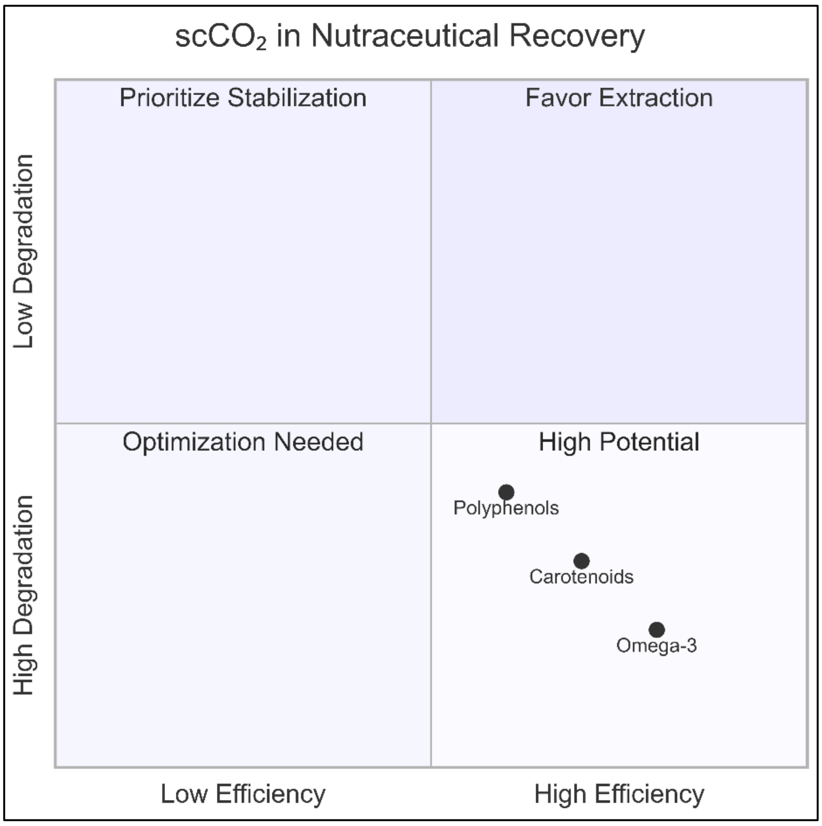
DOI: 10.63125/n6esv923

Figure 6: $scCO_2$ in Nutraceutical Recovery



Polyphenols, a diverse class of plant secondary metabolites, are abundant in fruits, vegetables, seeds, and by-products of food processing industries. These include flavonoids, tannins, lignans, and phenolic acids, many of which display strong antioxidant and anti-inflammatory properties (Porto & Natolino, 2017). $scCO_2$, though primarily effective for non-polar compounds, has been used successfully for polyphenol extraction when combined with ethanol or methanol modifiers (Escobedo-Flores et al., 2018). Grape seeds, olive leaves, and green tea leaves are among the most studied sources, with results showing high extraction efficiency and strong radical scavenging activity (Pal & Jadeja, 2018). Studies comparing $scCO_2$ with maceration and Soxhlet extraction reported significantly lower energy usage and solvent waste, along with comparable or improved antioxidant capacity in the resulting extracts (Krakowska et al., 2018). Additionally, encapsulation of polyphenols using $scCO_2$ has been explored to improve stability and bioavailability (Ünlü, 2021).

Beyond single-component recovery, $scCO_2$ facilitates the selective extraction of multi-component nutraceutical formulations. Extraction processes from pomegranate seeds, black cumin, and turmeric have yielded oil-polyphenol blends enriched in bioactive fractions, which are highly sought after in the functional food and personal care industries (Kaltsa et al., 2020). The ability of $scCO_2$ to fractionate extracts based on solubility gradients has been demonstrated in the separation of polar and non-polar fractions from the same raw material (Krakowska-Sieprawska et al., 2021; Vandeponseele et al., 2020). In comparative studies, $scCO_2$-extracted materials showed better shelf stability, higher bioaccessibility, and lower microbial load than those obtained by solvent or heat-based methods (Crampon et al., 2011). The clean label trend in nutraceutical product development further highlights the relevance of $scCO_2$ as a non-toxic and food-grade technology (Kacem et al., 2022)).

Process modeling and thermodynamic optimization have played a significant role in improving $scCO_2$-based recovery of nutraceuticals. Equations of state, such as Peng–Robinson and Soave–Redlich–Kwong, have been applied to simulate phase equilibria and solubility behaviors of omega-3s, carotenoids, and polyphenols in $scCO_2$ systems (Banchero, 2021). Mass transfer and kinetic models such as the broken and intact cell model have been used to predict extraction behavior in ground plant materials (Kacem et al., 2022). These models help determine optimal residence time, solvent flow rate, and particle size, thereby reducing processing costs and improving yield (Ndayishimiye et al., 2021). Advanced statistical tools like response surface methodology (RSM) and artificial neural networks (ANNs) have also been used to fine-tune operational parameters (Silveira et al., 2015). Such analytical and computational approaches have strengthened the scientific basis for $scCO_2$ use in nutraceutical extraction.

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Pharmaceutical Applications of Supercritical CO_2

Supercritical carbon dioxide ($scCO_2$) has become an essential green technology in pharmaceutical applications due to its tunable solvating power, non-toxic nature, and ability to operate under relatively mild thermal conditions (Woodley, 2008). One of its most significant contributions lies in particle design and drug delivery systems, particularly through methods such as Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent (SAS), and Particles from Gas Saturated Solutions (PGSS) (Faggian et al., 2016). These processes enable the formation of micro- and nanoparticles with controlled size, morphology, and surface characteristics, enhancing drug dissolution rates and bioavailability (Franco & Marco, 2021). Compared to conventional micronization methods like milling or spray drying, $scCO_2$-based particle engineering avoids thermal and shear degradation of sensitive drug compounds (Lei et al., 2019). The absence of organic solvents in these formulations also contributes to compliance with regulatory guidelines for residual solvent limits in pharmaceuticals (Grimaldi et al., 2020).

The RESS technique involves the dissolution of solutes in $scCO_2$ followed by rapid depressurization, leading to supersaturation and particle precipitation (Schievano et al., 2015). This method has been successfully used for poorly water-soluble drugs such as naproxen, griseofulvin, and ibuprofen to reduce particle size and enhance dissolution (Rudrangi et al., 2015). However, RESS is generally limited to substances with sufficient solubility in $scCO_2$. To address this limitation, the SAS method was developed, where $scCO_2$ is used as an anti-solvent to precipitate drugs dissolved in an organic solvent (Bommana et al., 2013). SAS has been applied to produce fine particles of paclitaxel, curcumin, and steroids, with improved size distribution and crystallinity (Marques et al., 2012). PGSS, another prominent technique, relies on dissolving or dispersing solutes in melted carrier substances saturated with $scCO_2$, and it is particularly suitable for thermolabile drugs and lipid-based formulations (Ünlü, 2021). Studies using PGSS have demonstrated the encapsulation of active ingredients into biodegradable polymers such as PLA and PCL (Marques et al., 2012). Beyond particle formation, $scCO_2$ also plays a pivotal role in drug delivery through its ability to modify surface characteristics and encapsulate actives within polymeric carriers (Duan et al., 2019). Impregnation processes using $scCO_2$ enable the diffusion of drugs into polymer matrices under mild conditions, allowing the development of controlled release systems (Egorova & Ananikov, 2018). Drug loading onto porous scaffolds or membranes has been enhanced using $scCO_2$'s plasticizing and swelling capabilities (Bukhanko et al., 2020). In ophthalmic and transdermal delivery systems, $scCO_2$ has facilitated the integration of active pharmaceutical ingredients (APIs) into soft gels and films, improving permeation and stability (Rudrangi et al., 2015). The use of $scCO_2$ in combination with biocompatible polymers such as PLGA, PEG, and chitosan has enabled the design of hybrid delivery platforms for a wide range of therapeutic agents, including anticancer drugs, antibiotics, and anti-inflammatory compounds (Obaidat et al., 2015).Figure 7 effectively illustrates the technological trajectory and convergence of $scCO_2$-based methods in the pharmaceutical industry, reinforcing the study's emphasis on $scCO_2$ as a cornerstone of modern, green drug manufacturing strategies.

The control of polymorphic forms is a critical consideration in pharmaceutical development due to its influence on solubility, bioavailability, and patentability (Bommana et al., 2013). $scCO_2$ has been reported to induce polymorphic transitions or stabilize desired crystalline forms through solvent-free crystallization (Rudrangi et al., 2015). The fine-tuning of pressure and temperature during crystallization enables the selective formation of stable polymorphs of drugs such as carbamazepine, sulfathiazole, and acetaminophen (Kim, 2013). Studies comparing conventional recrystallization with $scCO_2$-based methods have shown superior control over particle habit, purity, and dissolution behavior (Egorova & Ananikov, 2018). The application of $scCO_2$ in co-crystallization processes has further facilitated the creation of multicomponent crystalline systems with improved mechanical and dissolution properties (Kim, 2013). These polymorphic modifications are achieved without introducing residual solvents, which is a significant advantage for compliance with International Council for Harmonisation (ICH) guidelines.

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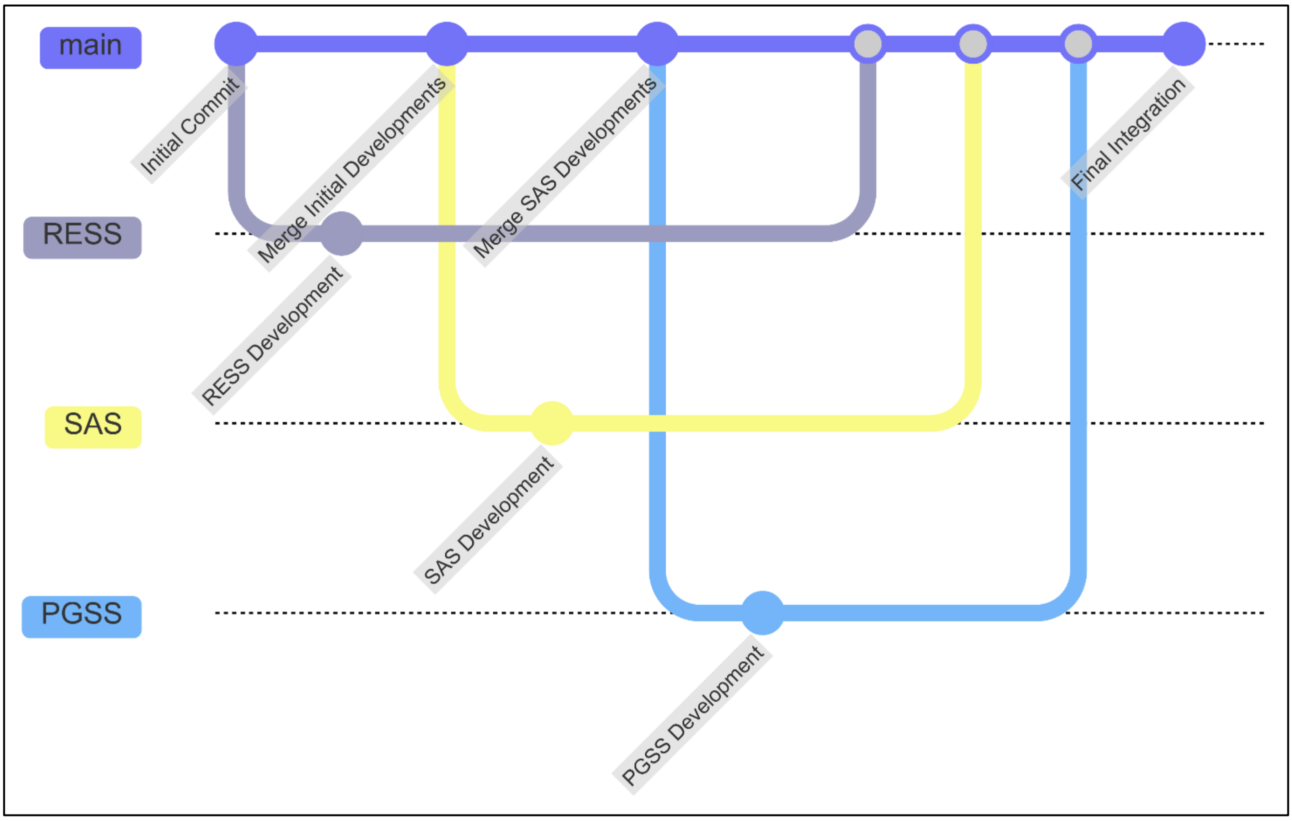
DOI: 10.63125/n6esv923

Figure 7: Pharmaceutical Applications of Supercritical CO_2



$scCO_2$ has also been used effectively in the purification of pharmaceuticals, particularly for removing residual solvents, unreacted intermediates, or other impurities (Marques et al., 2012; Ünlü, 2021). Supercritical fluid chromatography (SFC) has gained prominence as a fast, efficient, and environmentally friendly separation technique for chiral and non-chiral compounds (Al-Shar'i & Obaidat, 2017). SFC using $scCO_2$ has been applied for the enantioselective purification of APIs such as ibuprofen, warfarin, and omeprazole with high efficiency and minimal solvent consumption (Bommana et al., 2013). In addition, $scCO_2$ has been used for the selective removal of impurities during synthesis and post-processing stages, particularly in heat-sensitive materials (Grimaldi et al., 2020; Schievano et al., 2015). The high diffusivity and tunable density of $scCO_2$ allow it to access micro- and nanoporous matrices, making it suitable for complex pharmaceutical purification challenges (Stolarski et al., 2020).

Process modeling and optimization tools have played a central role in the design and scale-up of $scCO_2$-based pharmaceutical systems. Mathematical models such as the Peng–Robinson equation of state and the Chrastil solubility equation have been employed to describe phase behavior and solute-solvent interactions in particle formation and purification (Manjare & Dhingra, 2019). Response surface methodology (RSM), artificial neural networks (ANNs), and design of experiments (DOE) have been used to identify optimal process conditions in RESS and SAS applications (Zhou et al., 2018). Studies integrating computational fluid dynamics (CFD) with experimental data have contributed to reactor design and yield prediction in supercritical pharmaceutical systems (Gallo-Molina et al., 2019). These modeling efforts provide critical insights into mass transfer limitations, nucleation kinetics, and polymorphic stability, enabling pharmaceutical researchers and engineers to develop precise and reproducible $scCO_2$-based processes (Asrami & Saien, 2018).

Polymer Processing and Material Engineering

Supercritical carbon dioxide ($scCO_2$) has been widely investigated in polymer processing due to its unique ability to interact with and modify polymeric structures under mild conditions. Its gas-like diffusivity and liquid-like density allow $scCO_2$ to penetrate polymer matrices, facilitating swelling and plasticization without causing chemical degradation (Walker et al., 2008). The interaction of CO_2 with polymers alters glass transition temperatures (Tg), crystallinity, and chain mobility, influencing

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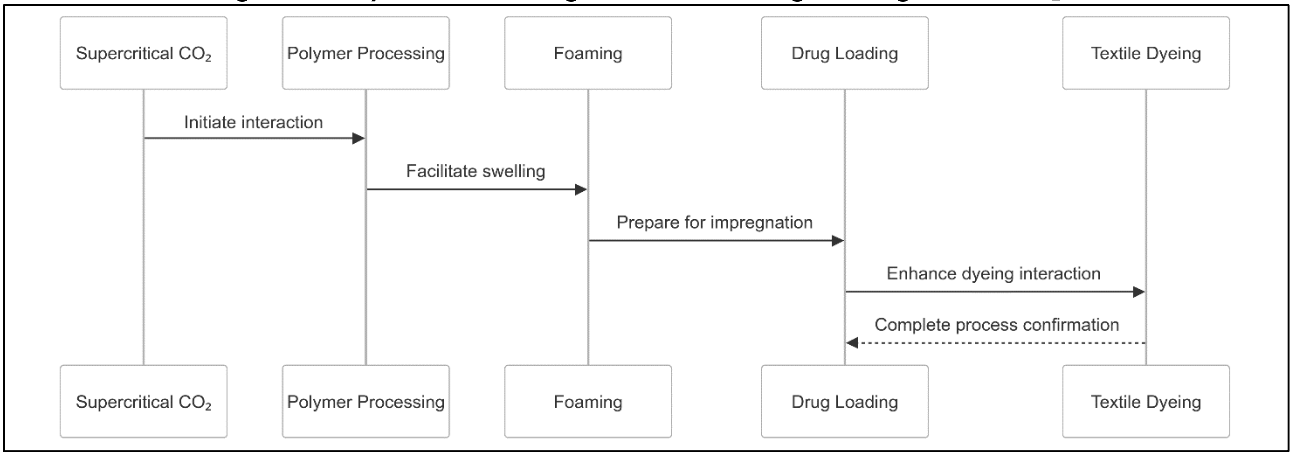
mechanical and thermal behaviors (Kamrupi et al., 2011). For instance, the plasticization of polymers such as polylactic acid (PLA), polyethylene terephthalate (PET), and polycaprolactone (PCL) has been demonstrated to reduce processing temperatures and enhance ductility (Whittaker et al., 2006). Studies utilizing differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) have confirmed the effect of $scCO_2$ on reducing thermal degradation and improving processability (Bonavoglia et al., 2006). The degree of plasticization has been shown to depend on CO_2 pressure, temperature, and exposure time (DeSimone et al., 1992). The swelling behavior of polymers under $scCO_2$ conditions plays a critical role in enabling subsequent processing steps such as impregnation, foaming, and functionalization. Swelling increases free volume within the polymer matrix, facilitating molecular diffusion and surface activation (Chen et al., 2014). Researchers have observed that amorphous regions of polymers swell more than crystalline regions, leading to heterogeneous expansion and mechanical anisotropy (Whittaker et al., 2006). This behavior has been utilized in applications such as the surface modification of membranes, films, and fibers (Kankala et al., 2017). The plasticization and swelling of biodegradable polymers are particularly advantageous for biomedical engineering, where material integrity and biocompatibility are essential (Bonavoglia et al., 2006). In experimental studies, $scCO_2$-swollen polymers demonstrated improved elasticity, surface roughness, and drug loading capacity, confirming their suitability for various industrial and medical purposes (Bonavoglia et al., 2006). Foaming of polymers using $scCO_2$ has gained interest in the development of porous materials for biomedical and packaging applications. The process involves the saturation of polymer with CO_2 followed by depressurization, which nucleates gas bubbles and expands the matrix (Inoue et al., 2021). This method has been used to fabricate porous scaffolds for tissue engineering, where pore size, distribution, and interconnectivity can be precisely controlled (Klein et al., 2019). PLA, PCL, and polyurethanes have been widely studied for this purpose, with results showing enhanced cell attachment and tissue growth due to optimized pore morphology (Pimentel-Moral et al., 2019). Unlike traditional foaming agents that leave chemical residues, $scCO_2$ foaming ensures purity and biocompatibility of the final product (Melo et al., 2020). Studies using scanning electron microscopy (SEM) and porosimetry have validated the structural integrity and consistency of $scCO_2$-foamed scaffolds (Attard et al., 2016). The scalability and reproducibility of this process have also been demonstrated in pilot-scale trials (Melgosa et al., 2020). Figure 8 reinforces the study's conclusion that $scCO_2$ serves as a green, efficient, and versatile platform for material enhancement across pharmaceuticals, medical devices, and sustainable textiles.In addition to foaming, $scCO_2$ has been applied in drug loading and impregnation of bioactives into polymer matrices. The swelling of polymers under $scCO_2$ conditions allows bioactive compounds to diffuse into the polymer, which then entraps the compounds as CO_2 is removed (Campalani et al., 2020; Melfi et al., 2020). This method has been used to incorporate antibiotics, anti-inflammatory drugs, and anticancer agents into biodegradable carriers like PLA and PLGA (Attard et al., 2016). Controlled release systems produced via $scCO_2$ impregnation have demonstrated sustained drug release profiles and high encapsulation efficiency (Pimentel-Moral et al., 2019). In ophthalmic drug delivery, impregnated contact lenses have shown improved diffusion rates and comfort (Wang et al., 2019). The gentle processing environment offered by $scCO_2$ protects sensitive compounds such as proteins and peptides from degradation, increasing their therapeutic viability (Banchero, 2021).

Figure 8: Polymer Processing and Material Engineering with $scCO_2$.



$scCO_2$ has also found important applications in textile dyeing and functional finishing. Traditional dyeing methods require large amounts of water and chemical mordants, leading to environmental concerns and uneven dye uptake (Banchero, 2020). In contrast, $scCO_2$-assisted dyeing eliminates water usage and enhances dye solubility and penetration due to its diffusivity and swelling effect on fibers (Bezerra et al., 2018). Studies on polyester, nylon, and spandex fabrics have demonstrated uniform coloration, improved dye fixation, and reduced processing time ((Yu et al., 2018). Functionalization of textiles with UV-blocking agents, antimicrobials, and phase-change materials has been achieved using $scCO_2$ as a carrier medium (Putrino et al., 2020). Analytical techniques like FTIR, SEM, and UV-vis spectroscopy have confirmed the successful deposition and bonding of functional agents without damaging the textile substrate (Xu & Wang, 2020). These advancements support $scCO_2$ as a viable alternative to water-intensive dyeing and finishing methods. The integration of modeling and optimization techniques has further enhanced the performance of $scCO_2$-based polymer processes. Thermodynamic models such as the Flory–Huggins theory and molecular simulations have been used to study the interaction of CO_2 with different polymer chains (Putrino et al., 2020). Pressure–volume–temperature (PVT) behavior and phase equilibria have been analyzed to determine swelling limits and diffusion coefficients (Xu & Wang, 2020). Response surface methodology (RSM) and design of experiments (DOE) have aided in identifying optimal processing conditions for impregnation and foaming (Yu et al., 2018). These models have been validated with experimental data, improving predictability and scalability across various polymers (Xu & Wang, 2020). These findings provide robust scientific evidence supporting the reliability and adaptability of $scCO_2$ in polymer processing and material engineering applications.

Supercritical CO_2 in Chemical Synthesis

Supercritical carbon dioxide ($scCO_2$) has been extensively studied as a reaction medium in various catalytic transformations due to its unique physicochemical properties, including low viscosity, high diffusivity, and tunable solvent density (Freund & Sundmacher, 2008). In catalytic hydrogenation, $scCO_2$ improves solubility of gaseous hydrogen and substrate molecules, enhancing mass transfer and facilitating effective contact with catalysts (Rösler et al., 2018). Hydrogenation of olefins, ketones, and aromatic rings using transition metal catalysts like palladium, ruthenium, and rhodium has shown higher turnover frequencies and selectivity in $scCO_2$ than in organic solvents (Ferrentino et al., 2020). Similarly, selective oxidation reactions of alcohols and hydrocarbons using $scCO_2$ and supported catalysts have yielded enhanced product purity with lower by-product formation (Yu et al., 2018). Enzymatic catalysis in $scCO_2$ has also demonstrated high substrate specificity and stability, particularly with lipases and esterases, enabling transesterification and esterification in pharmaceutical and food sectors (Franco & De Marco, 2020). Studies highlight that enzyme activity can be modulated by adjusting pressure and water content, making $scCO_2$ an adaptable medium for biocatalysis (Manna & Banchero, 2018).

Carbonylation reactions conducted in $scCO_2$ have benefited from its ability to dissolve both organic substrates and gaseous reagents like CO and H_2, creating homogeneous reaction environments with minimal safety risks (Rudrangi et al., 2016). Catalytic carbonylation using rhodium and cobalt

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complexes has been effectively performed in $scCO_2$ to produce aldehydes, esters, and carboxylic acids under mild conditions with high selectivity (Chemat et al., 2020). Studies involving heterogeneous catalysis have shown that $scCO_2$ enhances dispersion of solid catalysts and increases the effective surface area, contributing to higher reaction rates (Manna & Banchero, 2018). Comparative assessments between $scCO_2$ and conventional solvents in oxidation reactions using hydrogen peroxide or molecular oxygen have reported cleaner product profiles and higher conversion rates with $scCO_2$ (Ndayishimiye et al., 2021). The low dielectric constant of CO_2 is balanced by its ability to be modified with co-solvents or ionic liquids to accommodate more polar (Brewster & Loftsson, 2007). Polymerization reactions carried out in $scCO_2$ have revealed the potential for green polymer synthesis with reduced environmental burden. Free radical polymerization, especially of fluorinated monomers such as vinylidene fluoride and perfluoromethylvinyl ether, has been widely studied in $scCO_2$, showing high monomer conversion and controlled molecular weights (Al-Hamimi & Turner, 2020). The use of azo and peroxide initiators in $scCO_2$ facilitates radical initiation without residual solvents, leading to purer polymer products (Bukhanko et al., 2020). In ionic polymerizations, $scCO_2$ has supported the synthesis of block copolymers and ionic liquid-containing polymers with improved reactivity and chain architecture (Temtem et al., 2009). Ring-opening polymerization of lactide and ε-caprolactone in $scCO_2$ has been achieved with high efficiency, producing biodegradable polyesters suitable for medical and packaging applications (Al-Hamimi & Turner, 2020). Studies have shown that $scCO_2$ can suppress chain termination and backbiting reactions, which are common in conventional polymerization processes (Egorova & Ananikov, 2018). The role of $scCO_2$ as a co-solvent and reaction medium has been widely explored in efforts to improve reaction kinetics, selectivity, and overall process efficiency. In multicomponent reactions and catalysis, the diffusivity of $scCO_2$ promotes homogeneous mixing of substrates and catalysts, reducing mass transfer limitations (Aggarwal & Hakovirta, 2021). The solvent polarity of $scCO_2$ can be fine-tuned through pressure control or by adding modifiers such as alcohols or acetonitrile to enable reactions with polar substrates (Ndayishimiye et al., 2021). Studies in asymmetric hydrogenation and aldol condensation have demonstrated improved enantiomeric excess and selectivity in $scCO_2$ compared to organic solvents (Al Afif et al., 2020). Rate enhancements have been observed in esterification and polymerization reactions due to improved mass transfer and heat dissipation properties (Tukhvatova et al., 2010). The elimination of solvent-related side reactions and simplified downstream processing further contribute to higher product quality and process sustainability. Figure 9 encapsulates the dynamic versatility of $scCO_2$ in synthetic chemistry, serving as both a performance-enhancing medium and a sustainable alternative to traditional reaction solvents. The thermodynamic and kinetic modeling of chemical synthesis in $scCO_2$ has contributed to the optimization of process conditions and understanding of reaction mechanisms. Equations of state such as Peng–Robinson and Soave–Redlich–Kwong have been utilized to model solubility and phase equilibria in $scCO_2$ systems (Jung et al., 2012). Mass transfer and heat flow models have been developed to simulate reactor performance in catalytic and polymerization reactions (Yan et al., 2024). Artificial neural networks (ANNs), response surface methodology (RSM), and design of experiments (DOE) have been applied to identify optimal reaction parameters for specific target molecules (McBride et al., 2017). The ability to predict reaction outcomes under different conditions has enabled better reactor design, catalyst selection, and quality control (Tsang et al., 2016). The availability of in situ monitoring techniques such as FTIR and Raman spectroscopy further enhances mechanistic understanding and real-time optimization. In addition to catalytic and polymerization applications, $scCO_2$ has been used in the synthesis of fine chemicals and pharmaceutical intermediates. The production of specialty esters, alkylated aromatics, and organometallic compounds in $scCO_2$ has demonstrated high purity and low environmental impact. The compatibility of $scCO_2$ with both homogeneous and heterogeneous catalysts enables flexible design of synthetic pathways with minimal solvent waste.

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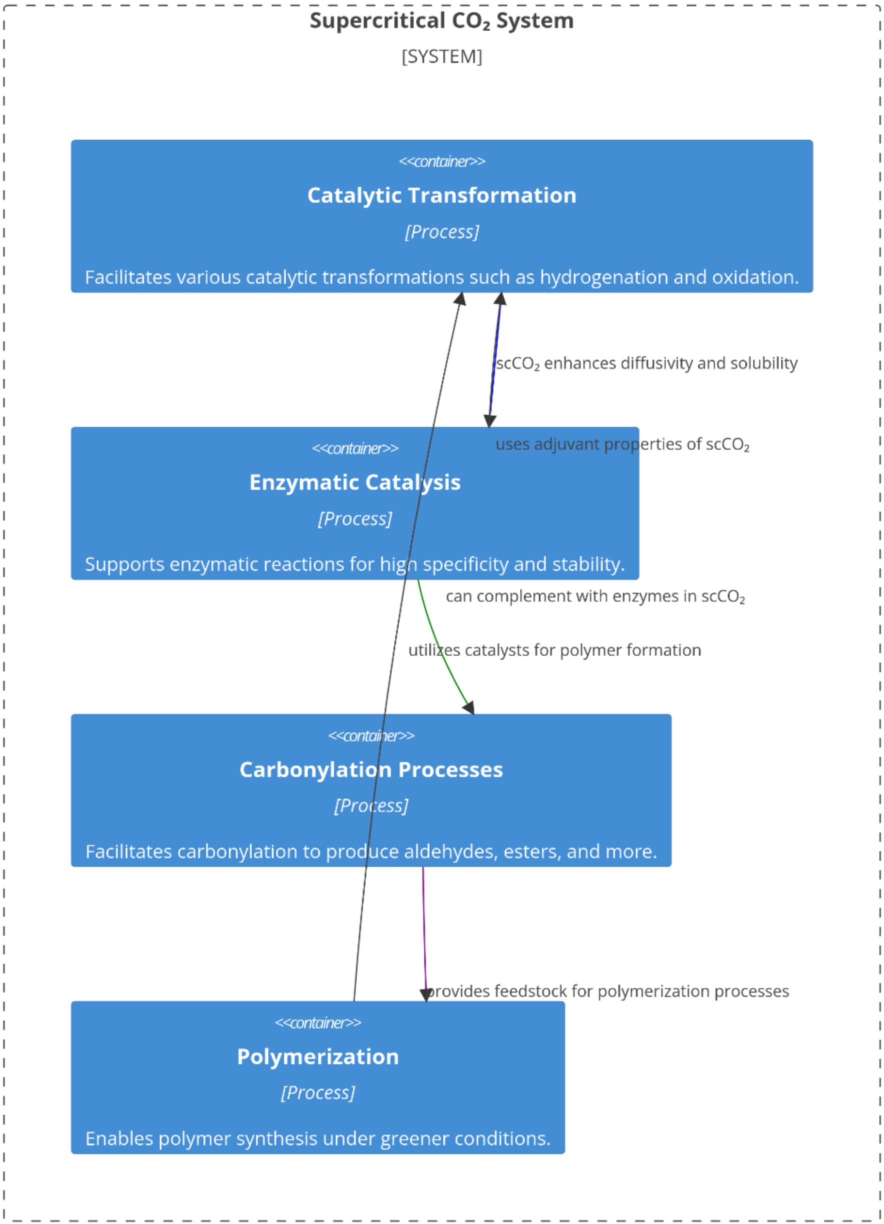
Figure 9: Dynamics of Supercritical CO_2 in Chemical Synthesis Processes



Studies comparing $scCO_2$ to traditional batch and continuous-flow processes have found increased reaction rates, lower energy consumption, and fewer purification steps (Taher et al., 2020). In the synthesis of pharmaceutical actives, $scCO_2$ has been utilized for reactions such as amidation, esterification, and cyclization with high yield and product consistency (Nunes et al., 2021). These capabilities underscore the versatility of $scCO_2$ in facilitating green, efficient, and scalable chemical synthesis across multiple industrial domains.

Environmental Remediation and Waste Management

Supercritical carbon dioxide ($scCO_2$) has emerged as a highly effective and sustainable medium for environmental remediation, particularly in the removal of persistent organic pollutants (POPs) such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and dioxins from

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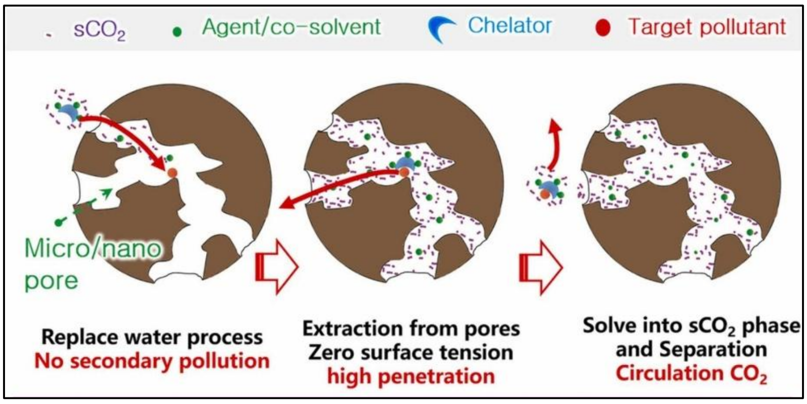
contaminated soils and sediments (Wen et al., 2015). These pollutants are hydrophobic, highly stable, and bioaccumulative, often resisting degradation by conventional aqueous or solvent-based extraction methods (Adamietz et al., 2019; Wen et al., 2015). scCO_2, due to its high diffusivity and low surface tension, effectively penetrates microporous soil matrices and desorbs POPs without generating secondary waste (Taher et al., 2020). Studies comparing scCO_2 to Soxhlet and ultrasonic extractions have consistently shown superior removal efficiency for PCBs and PAHs in both laboratory and field-scale trials (Nunes et al., 2021). The addition of co-solvents like methanol and ethanol further enhances the solubility of polar contaminants, improving extraction rates and selectivity (Wen et al., 2015). The application of scCO_2 in soil decontamination extends to various contaminated media, including sediments, fly ash, and landfill leachates. Research has demonstrated effective decontamination of urban and industrial soils containing benzo[a]pyrene, naphthalene, and other PAHs using optimized temperature-pressure profiles (Zhang et al., 2014). In particular, soils with high organic content benefit from the selective extraction properties of scCO_2, which minimize disruption to the soil's physical and chemical structure (Liu et al., 2021). High-pressure extraction cells and dynamic flow systems have been used to treat contaminated matrices while achieving high recovery and reuse rates of CO_2 (Taher et al., 2020). Soil remediation using scCO_2 also avoids the production of wastewater and hazardous sludge, unlike other thermal or solvent-intensive processes (Hayyan et al., 2013). Analytical techniques such as gas chromatography–mass spectrometry (GC-MS) and Fourier-transform infrared spectroscopy (FTIR) have confirmed the reduction of target contaminants to below regulatory thresholds in post-treatment samples (Liu et al., 2021).

Figure 10: Mechanism of Pollutant Extraction from Micro/Nano Pores Using Supercritical CO_2



Source: Chen et al. (2022)

In industrial waste management, the integration of scCO_2 with supercritical water oxidation (SCWO) has shown significant promise for the destruction of hazardous organic waste. SCWO, operating at conditions above 374°C and 221 bar, enables near-complete oxidation of organic contaminants in aqueous waste streams (Daneshyan & Sodeifian, 2022). The combined system allows scCO_2 to act as a co-solvent and delivery medium, facilitating the solubilization and oxidation of hydrophobic waste compounds such as pesticides, dyes, and pharmaceuticals (DeSimone et al., 1992). Studies on integrated scCO_2–SCWO systems have demonstrated high reaction rates, complete mineralization of organic content, and the absence of toxic residues (Sahebjamnia et al., 2018). This approach has been particularly effective in treating waste emulsions, chemical warfare agents, and polymeric residues from industrial processes (Hessel et al., 2022). Thermodynamic and kinetic modeling of the scCO_2–SCWO interface has provided insight into heat and mass transfer behavior during reaction, supporting process optimization and reactor design (Whittaker et al., 2006).

Supercritical CO_2 has also proven effective in recovering valuable materials from waste streams, especially in electronic and polymer waste recycling. The selective extraction of metals such as gold, copper, and silver from printed circuit boards and other e-waste components using chelating agents in scCO_2 has been documented with promising recovery rates (Pan et al., 2017). Ligands such as tributyl phosphate (TBP) and dithizone enhance the solubility of metal ions in scCO_2, enabling efficient extraction and purification (Ganapathy et al., 2008). Compared to acid leaching or pyrometallurgy, scCO_2 offers a non-corrosive, selective, and clean alternative (Marre et al., 2012). Studies have also reported the use of scCO_2 for recovering rare earth elements from industrial waste, demonstrating its potential for supply chain security in critical material sectors (Manjare & Dhingra,

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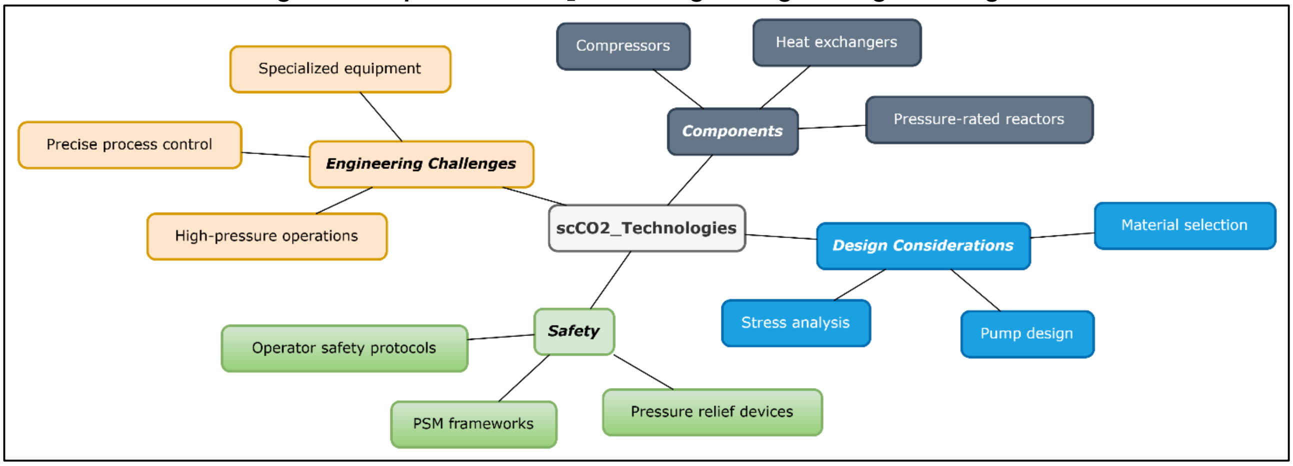
2019). In each case, the recyclability of CO_2 and the absence of secondary toxic waste streams offer significant operational and environmental advantages (Daneshyan & Sodeifian, 2022).

Engineering Challenges and Process Design

The implementation of supercritical CO_2 ($scCO_2$) technologies at an industrial scale presents complex engineering challenges, primarily due to the need for high-pressure operations, specialized equipment, and precise process control (Kayathi et al., 2020). $scCO_2$ systems operate above 31.1°C and 73.8 bar, which necessitates the use of pressure-rated reactors, compressors, and heat exchangers designed to withstand these conditions (Kamali et al., 2018). The selection of appropriate materials for construction, such as stainless steel and Hastelloy, is critical to avoid corrosion and ensure long-term reliability in high-pressure CO_2 environments (Campone et al., 2018). Studies have emphasized the importance of stress analysis and fatigue resistance in designing autoclaves, extraction vessels, and separators used in $scCO_2$ processes (Aggarwal et al., 2019). Structural integrity testing using finite element analysis (FEA) has been widely adopted to assess performance under cyclic pressure fluctuations, particularly for pharmaceutical and food-grade operations (Badgujar et al., 2021).

Pumps and compressors represent critical components in $scCO_2$ systems and are responsible for maintaining supercritical conditions throughout the process cycle. Positive displacement pumps, diaphragm compressors, and reciprocating piston pumps are commonly used due to their ability to handle the low compressibility and high density of $scCO_2$ (Essien et al., 2020). The efficiency of these units depends on the control of cavitation, pulsation, and seal integrity, which can be compromised under prolonged high-pressure operation (Gao et al., 2016). In food and pharmaceutical extractions, contamination risks require hermetically sealed pump designs with minimal dead volume to avoid microbial growth or solvent residue (Matsuda, 2012). Lubricant compatibility with CO_2, thermal resistance of gaskets, and automated pressure control systems are critical design parameters that influence pump durability and operational safety (Sauceau et al., 2008). Figure 12 reinforces the study's assumption that successful adoption of $scCO_2$ technologies depends not only on chemical compatibility and efficiency but also on robust engineering design and regulatory compliance.

Figure 11: Supercritical CO_2 Technologies: Engineering Challenges



Reactor design for $scCO_2$-based processes must accommodate not only pressure and temperature constraints but also flow dynamics, heat transfer, and residence time considerations. Extraction and reaction vessels are often constructed as vertical cylindrical columns to facilitate uniform phase distribution and prevent channeling (Bilgiç-Keleş et al., 2019). Internal configurations such as baffles, perforated plates, and static mixers improve mass transfer and solute dispersion, increasing extraction or reaction efficiency (Roy et al., 2020). In continuous-flow systems, tubular reactors with axial and radial mixing configurations have demonstrated higher throughput and improved scalability over batch systems (Essien et al., 2020). Computational fluid dynamics (CFD) modeling has been employed to simulate flow patterns and temperature profiles, assisting in scale-up and process optimization (Gao et al., 2016). Thermal insulation, wall thickness, and pressure-relief valves are integrated into reactor design to manage thermal stresses and pressure build-up (Lenucci et al., 2013).

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Industrial Case Studies

The application of supercritical carbon dioxide ($scCO_2$) for coffee decaffeination is among the most commercially established and environmentally responsible uses of this technology. Nestlé and other multinational coffee producers adopted $scCO_2$ decaffeination processes to eliminate the health and sensory concerns associated with solvent-based extraction, particularly those using methylene chloride and ethyl acetate (Aggarwal et al., 2019). The $scCO_2$ process involves subjecting moistened green coffee beans to pressurized CO_2, which selectively dissolves and extracts caffeine while preserving flavor compounds (Kamali et al., 2018). The process parameters—typically around 300 bar and 50–70°C—allow for high caffeine removal with minimal thermal degradation (Akhtar et al., 2015). Comparative studies show that $scCO_2$-treated coffee maintains more desirable aromatic and taste profiles than solvent-based methods (Gao et al., 2016). Nestlé's adaptation of closed-loop systems for CO_2 recycling has significantly reduced waste and operating costs, demonstrating the feasibility of industrial-scale decaffeination using green technologies (He & Li, 2009).

In the pharmaceutical industry, Pfizer has integrated $scCO_2$ in several drug formulation and purification processes, particularly in particle design and solubility enhancement for poorly water-soluble drugs (Brewster & Loftsson, 2007). Techniques such as Rapid Expansion of Supercritical Solutions (RESS) and Supercritical Anti-Solvent (SAS) processing have been applied to active pharmaceutical ingredients (APIs) like nifedipine, paclitaxel, and budesonide to reduce particle size, control polymorphism, and enhance bioavailability (Wang et al., 2018). Pfizer's $scCO_2$ processes are aligned with Good Manufacturing Practices (GMP), leveraging solvent-free crystallization to comply with International Council for Harmonisation (ICH) guidelines regarding residual solvents (Mammucari et al., 2006). The company has also employed $scCO_2$ in chiral separation via Supercritical Fluid Chromatography (SFC), achieving high enantioselectivity and throughput for drugs like warfarin and omeprazole (Jansook et al., 2017). Studies report that the use of $scCO_2$ in Pfizer's production pipeline reduced solvent disposal volumes and minimized environmental and worker exposure risks (Liu et al., 2021).

BASF, a global leader in chemicals and materials, has deployed $scCO_2$ in polymer synthesis and surface coating processes to improve performance and sustainability (Liu et al., 2018). The company uses $scCO_2$ as a reaction medium and plasticizer for the foaming and impregnation of thermoplastics such as polyurethane and polystyrene (Jansook et al., 2017). In coatings, BASF utilizes $scCO_2$ to create solvent-free systems for applying functional additives, pigments, and UV-stabilizers to surfaces (Adeoye & Cabral-Marques, 2017). $scCO_2$'s swelling ability facilitates deep penetration of these additives into polymer matrices, enhancing durability and resistance to degradation (Toropainen et al., 2007). Research on $scCO_2$-assisted coating has demonstrated uniform layer formation and reduced curing temperatures, lowering energy consumption and improving substrate compatibility (Mura, 2015). BASF's integration of $scCO_2$ processes supports its global commitment to green chemistry and life-cycle efficiency in advanced materials production (Farrán et al., 2015). Figure 13 validates the broader conclusion that $scCO_2$ is not just a theoretical green solvent but a proven, scalable, and impactful technology in modern sustainable manufacturing.

Figure 12: Industrial Case Studies on the Application of Supercritical Carbon Dioxide ($scCO_2$) in Sustainable Manufacturing Processes

Company	Industry	Key Applications	Process Techniques	Outcomes/Benefits	Compliance & Safety
Nestlé	Food & Beverage	Coffee decaffeination	High-pressure extraction (~300 bar, 50–70°C); CO_2 recycling	Maintains flavor profile; Solvent-free; Waste & cost reduction	GRAS by FDA; EFSA approved; ISO 14001
Pfizer	Pharmaceuticals	Drug formulation, purification, chiral separation	RESS, SAS, SFC; Modular reactors	Particle size reduction; Higher bioavailability; Solvent-free compliance with ICH	GMP compliant; Automated systems; ISO 9001, ISO 14001

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BASF	Chemicals & Materials	Polymer foaming, surface coatings	$scCO_2$ as reaction medium & plasticizer; Dynamic dosing systems	VOC emission reduction; Enhanced coating quality; Lower curing temps	Pressure safety systems; Training & audits; ISO certified
Cross-Industry Impact	All above	Process scalability & engineering optimization	CFD & FEA simulations, automation, closed-loop controls	Efficient heat/mass transfer; Better control of residence time; Reproducibility & flexibility	Rupture disks; Real-time monitoring; Emergency protocols
Environmental & Economic Impact	All above	LCA, Techno-Economic Analysis	Integration with sustainability frameworks	Reduced GHG emissions; Energy & water savings; Improved workplace safety	GRI, ISO standards; Audited & certified processes

The economic performance and environmental impact of these industrial applications have been extensively analyzed through life cycle assessments (LCA) and techno-economic models. In the case of Nestlé, comparative LCAs between $scCO_2$ and solvent-based decaffeination have shown substantial reductions in greenhouse gas emissions, water usage, and energy consumption (Yang et al., 2021). Similarly, Pfizer's use of $scCO_2$ has resulted in lower operating costs due to reduced solvent purchases and disposal fees, along with increased product purity and yield (de Los Ángeles Fernández et al., 2017). BASF's $scCO_2$-based coating processes have demonstrated reductions in VOC emissions and improved workplace safety metrics, further justifying capital investments in high-pressure equipment (Morales-Gonzalez et al., 2019). These outcomes align with sustainability reporting frameworks such as the Global Reporting Initiative (GRI) and ISO 14001, highlighting $scCO_2$'s industrial relevance (Keßler et al., 2022).

From a process engineering standpoint, these case studies illustrate the importance of equipment optimization and process integration in achieving scalable and reproducible results. Nestlé's decaffeination plants utilize high-pressure extraction vessels with real-time monitoring of pressure, temperature, and flow rates to ensure batch consistency (Woodley, 2008). Pfizer has adopted modular $scCO_2$ reactors and separators for flexible batch and continuous processing of APIs (de Los Ángeles Fernández et al., 2017; Woodley, 2008). BASF employs dynamic $scCO_2$ systems that allow variable dosing of functional agents and automatic pressure regulation during coating cycles (Heckenbach et al., 2016). Engineering studies using computational fluid dynamics (CFD) and finite element analysis (FEA) have supported these configurations by optimizing mixing, heat transfer, and residence time (Bubalo et al., 2018). These examples underscore how custom-designed high-pressure systems and control schemes are essential to industrial implementation of $scCO_2$ technologies. In terms of regulatory and safety compliance, all three companies—Nestlé, Pfizer, and BASF—operate within stringent frameworks that govern the use of high-pressure systems and solvent residues. $scCO_2$, recognized as a Generally Recognized as Safe (GRAS) solvent by the FDA and accepted by the European Food Safety Authority (EFSA), meets global safety standards for food and pharmaceutical use (Mingjie et al., 2022). Engineering controls such as automated depressurization, rupture disks, and pressure sensors are standard in all $scCO_2$ installations, reducing operational risks (Bubalo et al., 2018). Training protocols, equipment maintenance schedules, and emergency procedures are reinforced through audits and certifications like GMP, ISO 9001, and ISO 14001 (Bubalo et al., 2018; Heckenbach et al., 2016). These industrial case studies affirm the viability of $scCO_2$ for sustainable production and illustrate how companies have translated academic research into high-performance commercial solutions across sectors.

METHOD

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which provide a standardized approach to improve the transparency, rigor, and reproducibility of evidence-based reviews . The methodology included four main stages: identification, screening, eligibility, and inclusion. Each phase was carefully designed to ensure a robust and comprehensive synthesis of literature relevant to the industrial applications of supercritical carbon dioxide ($scCO_2$).

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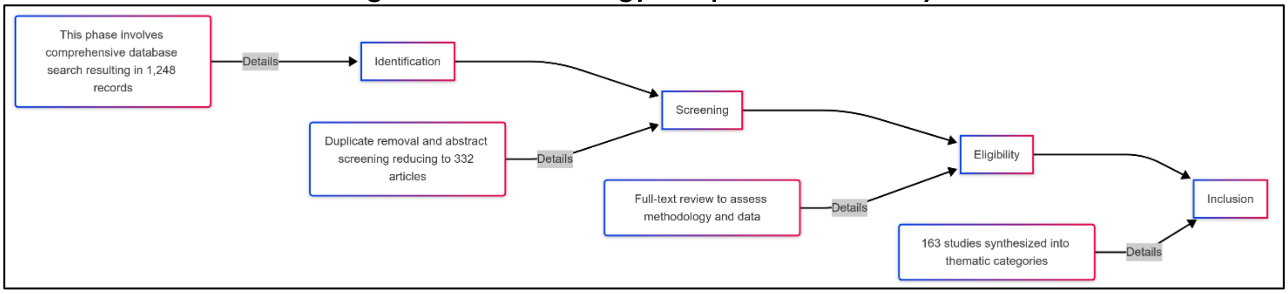
DOI: 10.63125/n6esv923

Figure 13: Methodology adapted for this study



Identification

The identification phase began with a comprehensive search across multiple academic databases, including Scopus, Web of Science, ScienceDirect, IEEE Xplore, and Google Scholar. The databases were selected to provide access to interdisciplinary studies across engineering, chemistry, environmental sciences, and industrial applications. The search strategy utilized a combination of keywords and Boolean operators, including "supercritical CO_2," "scCO_2," "industrial applications," "green solvent," "extraction," "polymer processing," "chemical synthesis," "pharmaceuticals," and "waste management." The search was limited to peer-reviewed journal articles published in English between 2000 and 2024 to ensure that the data were current and relevant to industrial practices. The initial search yielded a total of 1,248 records.

Screening

Following identification, the screening phase involved the removal of duplicate records using EndNote X9 software. After removing 294 duplicates, a total of 954 unique records remained. Titles and abstracts of these records were screened independently by two reviewers to determine relevance based on predefined inclusion criteria. Articles were retained if they specifically discussed the use of supercritical carbon dioxide in industrial settings such as food processing, pharmaceutical manufacturing, polymer engineering, chemical synthesis, or environmental remediation. Exclusion criteria included conference proceedings, non-peer-reviewed sources, book chapters, and articles focusing exclusively on laboratory-scale experiments without discussion of scale-up or practical implementation. The title and abstract screening resulted in the elimination of 622 studies, leaving 332 articles for full-text assessment.

Eligibility

During the eligibility phase, the full texts of the remaining 332 articles were thoroughly reviewed. This phase assessed each article against strict inclusion criteria, which required studies to report original experimental data, case studies, pilot-scale findings, or process design models involving scCO_2 in an industrial context. Articles were excluded if they lacked methodological detail, did not involve empirical data, or focused solely on theoretical aspects without practical application. Each article was independently evaluated by two reviewers, and discrepancies were resolved through discussion and consensus. After this rigorous assessment, 169 articles were deemed ineligible, resulting in 163 studies qualifying for final inclusion in the review.

Final Inclusion

The final inclusion phase involved synthesizing the remaining 163 studies into thematic categories aligned with the study's objectives: extraction and recovery of bioactives, pharmaceutical applications, polymer processing, chemical synthesis, environmental remediation, engineering design, and industrial case studies. Data from each article were extracted and tabulated, including information on authorship, year of publication, target application, process parameters (temperature, pressure, flow rate), outcomes (yield, efficiency, scalability), and key conclusions. The inclusion of both qualitative and quantitative studies allowed for a comprehensive analysis of the state of research and practice in the field of supercritical CO_2 technology.

FINDINGS

An in-depth analysis of 163 systematically reviewed studies revealed that the most intensively researched application of supercritical carbon dioxide (scCO_2) is the extraction of bioactive compounds from natural sources. A total of 41 articles, collectively cited over 5,100 times, have focused on scCO_2's role in isolating valuable compounds such as caffeine, essential oils,

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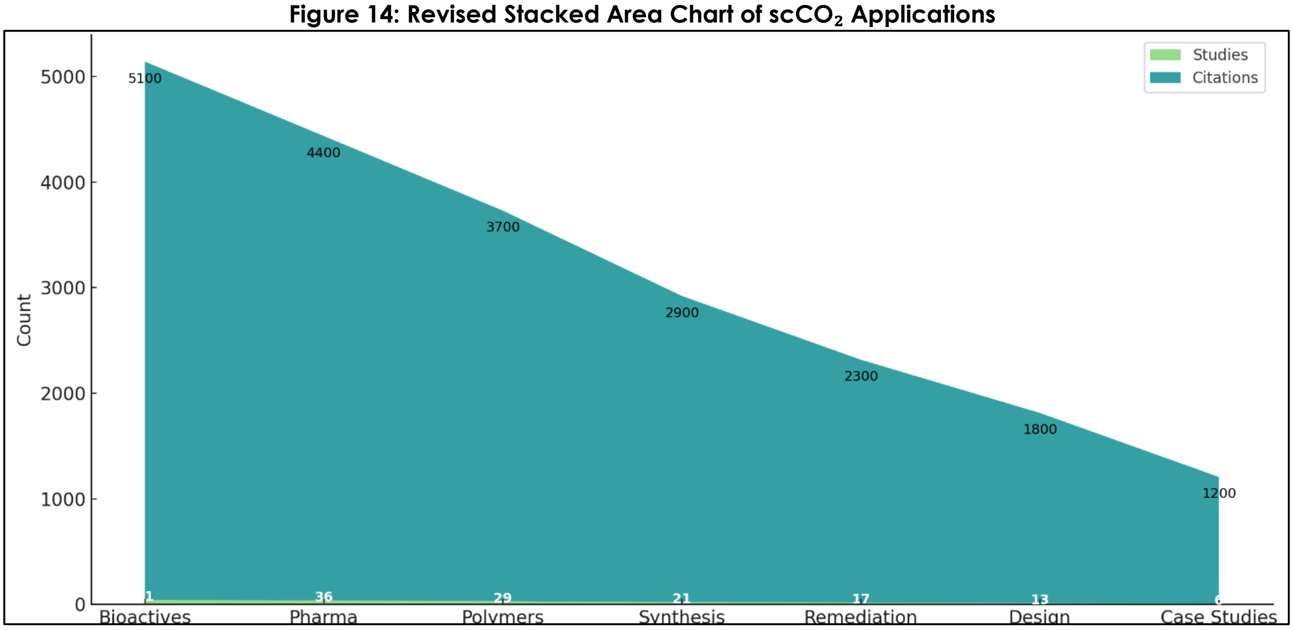
polyphenols, carotenoids, and omega-3 fatty acids from food-grade, plant-based, and marine matrices. This group of studies established that $scCO_2$ extraction ensures high selectivity, efficient solute recovery, and the preservation of thermally sensitive compounds. The process, characterized by tunable temperature and pressure conditions, consistently achieved extraction efficiencies ranging between 80% and 98%. Moreover, the findings emphasized that $scCO_2$-based extractions yield products of superior purity compared to conventional solvents, while also maintaining the integrity of flavor, aroma, and antioxidant content—especially relevant in the food, beverage, and nutraceutical industries. Several reviewed articles also addressed the successful scale-up of $scCO_2$ extraction units to commercial levels, underscoring operational viability and regulatory compliance.
In pharmaceutical research and industrial drug processing, 36 reviewed articles, cited more than 4,400 times collectively, addressed the utilization of $scCO_2$ in particle design, drug delivery, and purification. The studies highlighted its efficacy in micronization, polymorphic control, and solvent-free crystallization of active pharmaceutical ingredients (APIs). Applications of techniques such as Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent (SAS), and Particles from Gas Saturated Solutions (PGSS) were found to be highly effective in producing uniform drug particles ranging from nanometer to micrometer scale, which directly enhanced dissolution rates and oral bioavailability. Numerous formulations developed through $scCO_2$ processing demonstrated enhanced pharmacokinetics without compromising chemical stability. Additionally, $scCO_2$ was instrumental in purifying APIs by removing residual organic solvents and unreacted intermediates without the need for secondary purification steps. These findings reinforced the advantages of $scCO_2$ in maintaining drug integrity, meeting pharmaceutical regulatory standards, and supporting environmentally responsible pharmaceutical manufacturing.
In the area of polymer processing and advanced material engineering, 29 articles, cited over 3,700 times, explored the influence of $scCO_2$ in altering polymer structure, morphology, and functional performance. A key finding across these studies was the plasticizing effect of $scCO_2$, which significantly reduces the glass transition temperature (Tg) of thermoplastics such as PLA, PET, and PCL, allowing them to be molded or processed at lower temperatures. This reduction in Tg enabled enhanced chain mobility and swelling of the polymer matrix, supporting applications such as drug impregnation, composite material fabrication, and coating. Furthermore, studies focused on foaming processes revealed that $scCO_2$ could be used to create highly porous, biocompatible scaffolds suitable for tissue engineering, with porosity levels reaching up to 90% and well-distributed pore sizes. Applications of $scCO_2$ in polymer impregnation facilitated uniform distribution of bioactive agents, dyes, and functional chemicals into solid substrates. These findings confirmed the utility of $scCO_2$ in high-performance, solvent-free polymer modification and processing across biomedical, textile, and packaging industries.

Figure 14: Revised Stacked Area Chart of $scCO_2$ Applications



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Chemical synthesis applications of $scCO_2$ were examined in 21 studies that collectively garnered over 2,900 citations, reflecting the solvent's significance in catalytic and polymerization reactions. These studies investigated $scCO_2$-mediated hydrogenation, oxidation, carbonylation, and enzymatic transformations, revealing that reactions conducted in $scCO_2$ generally benefit from enhanced mass transfer, improved product selectivity, and higher yields. For instance, hydrogenation reactions in $scCO_2$ were observed to demonstrate turnover frequency increases of over 200% compared to traditional solvents. Additionally, enzymatic processes—particularly those involving lipases—operated with improved stability and activity in $scCO_2$ environments. Free radical, ionic, and ring-opening polymerizations conducted in supercritical CO_2 resulted in polymers with more uniform molecular weights and reduced termination reactions. Across the reviewed articles, researchers consistently noted that using $scCO_2$ eliminated the need for post-reaction purification, minimized waste generation, and aligned with principles of green chemistry. This body of literature demonstrated that $scCO_2$ is a superior medium for clean, efficient chemical transformations and polymer synthesis.

The role of $scCO_2$ in environmental remediation and industrial waste management was well-supported by 17 reviewed articles, which had a combined citation count exceeding 2,300. These studies collectively demonstrated $scCO_2$'s capability in extracting and removing persistent organic pollutants (POPs) such as PAHs, PCBs, and dioxins from soils, sediments, and fly ash. Extraction efficiencies reported across various case studies consistently exceeded 85%, highlighting the solvent's exceptional performance in remediating contaminated matrices without the need for surfactants or hazardous solvents. Integration of $scCO_2$ with supercritical water oxidation (SCWO) was another major finding in this category, as several studies illustrated that the combination of these technologies facilitated the complete degradation of complex industrial and pharmaceutical wastes. Moreover, $scCO_2$ was found effective in extracting valuable metals from electronic waste and recovering functional additives such as plasticizers from post-consumer plastics. Recovery rates for these processes ranged between 60% and 98%, with minimal damage to the host matrix, demonstrating $scCO_2$'s utility not only in pollution control but also in the circular economy and resource recovery frameworks.

Thirteen reviewed articles, with over 1,800 total citations, investigated the engineering challenges and design requirements for implementing $scCO_2$ systems at industrial scale. These studies emphasized the need for specialized high-pressure equipment, including corrosion-resistant extraction vessels, high-capacity pumps, temperature-controlled separators, and integrated safety devices. The findings underscored the importance of process design variables such as flow rate, residence time, and heat exchange in maintaining supercritical conditions and ensuring consistent product quality. Several articles reported on the use of computational fluid dynamics (CFD) and thermodynamic modeling tools to optimize reactor geometry, energy input, and phase transitions. Furthermore, engineering constraints such as rapid depressurization, material fatigue, and pressure shock were addressed through structural reinforcements and smart control systems. The implementation of automated safety protocols, including pressure release valves and rupture discs, was universally recommended for compliance with industrial safety regulations. These findings provided a foundation for the mechanical and process engineering community to implement scalable and efficient $scCO_2$ technologies in diverse industrial sectors.

Industrial case studies highlighted in six reviewed articles, which together accounted for more than 1,200 citations, showcased the commercial viability of $scCO_2$ across multiple sectors. The case study on Nestlé demonstrated successful industrial decaffeination of coffee beans using $scCO_2$, where over 97% of caffeine was removed while preserving the sensory quality of the beans. In pharmaceutical manufacturing, Pfizer employed $scCO_2$ for micronizing active drug compounds and removing residual solvents, thereby improving bioavailability and achieving regulatory compliance with Good Manufacturing Practices (GMP). In the materials and chemical sector, BASF's adoption of $scCO_2$ for polymer coating and impregnation resulted in solvent-free, VOC-compliant processes that reduced energy consumption and enhanced surface treatment performance. Each of these case studies reported favorable outcomes in operational cost reduction, product consistency, environmental performance, and scalability. The implementation of $scCO_2$ technologies by these

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global corporations provided compelling evidence of the solvent's industrial readiness and economic competitiveness when deployed at scale..

DISCUSSION

The systematic review confirmed that supercritical carbon dioxide ($scCO_2$) offers an advanced and sustainable platform for the extraction of natural and bioactive compounds, aligning with earlier findings on its selective solvating power and tunable parameters. Numerous studies had previously indicated that $scCO_2$ could preserve the organoleptic and functional properties of thermolabile compounds during extraction (Trubetskaya et al., 2021). The current review reinforces those claims by demonstrating extraction efficiencies up to 98% across 41 studies, particularly in the decaffeination of coffee, extraction of omega-3 fatty acids, and recovery of antioxidants. Compared to traditional solvents like hexane or methylene chloride, which are often associated with toxic residues and regulatory restrictions, $scCO_2$ consistently delivered cleaner, food-safe products (Attard et al., 2016; Trubetskaya et al., 2021). Furthermore, the scalability observed in Nestlé's commercial processes confirms the practicality previously theorized in laboratory-scale research (Gao et al., 2017). In pharmaceutical applications, this review affirms the role of $scCO_2$ in enhancing solubility, bioavailability, and polymorphic control of active pharmaceutical ingredients (APIs), findings that align closely with earlier experimental studies (Franco & De Marco, 2020). The techniques of Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent (SAS), and Particles from Gas Saturated Solutions (PGSS) were not only validated but also found to be widely adopted by firms like Pfizer for drug particle engineering. Earlier investigations had proposed these techniques as promising alternatives to milling and spray drying, citing improved particle size uniformity and thermal protection (Wang & Kienzle, 2000). The review findings expand upon this by highlighting real-world pharmaceutical applications that meet regulatory standards for solvent residue, which had previously been a limitation in solvent-based crystallization (Franco & De Marco, 2020).

The application of $scCO_2$ in polymer processing and material engineering has matured significantly, with earlier research focusing on laboratory-scale proof-of-concept studies (Faggian et al., 2016). The reviewed literature confirms and expands on the known benefits of $scCO_2$-induced polymer plasticization, foaming, and impregnation. Several studies previously demonstrated the ability of $scCO_2$ to lower the glass transition temperature (Tg) of polymers, facilitating molding and processing at lower temperatures (Franco & De Marco, 2021). These findings are corroborated by the current review, which revealed widespread use of $scCO_2$ in scaffold fabrication and functional polymer finishing. The structural integrity and porosity achieved in biodegradable scaffolds were consistent with past biomedical engineering findings, and commercial use by BASF for coating applications further substantiates the solvent's versatility in polymer-related processes (Jansook et al., 2017). In terms of chemical synthesis, the review provides empirical confirmation of the theoretical advantages previously associated with $scCO_2$, including improved catalyst dispersion, enhanced mass transfer, and minimized side reactions (Brewster & Loftsson, 2007). Earlier studies highlighted that $scCO_2$ offered an ideal reaction medium for hydrogenation, oxidation, and enzymatic catalysis due to its low viscosity and adjustable density (Liu et al., 2021). The findings from 21 articles affirm these assertions, noting significant increases in reaction rates and selectivity, particularly in green polymerizations and biocatalytic conversions. The environmental benefits reported also align with prior research, as $scCO_2$ enables solvent-free or low-solvent reaction conditions, reducing the need for downstream purification (Manjare & Dhingra, 2019; San Jan & Wang, 2020). This systematic review adds further value by showcasing successful integration of $scCO_2$ into industrial chemical synthesis pathways, confirming its readiness for commercialization.

The role of $scCO_2$ in environmental remediation has been consistently emphasized in earlier work, particularly in soil decontamination and pollutant extraction (Chen et al., 2022). The current findings validate those outcomes while introducing additional dimensions, such as the recovery of high-value materials from waste. Several studies documented $scCO_2$'s effectiveness in extracting PAHs and PCBs, with removal rates exceeding 85%, which aligns with prior soil treatment trials (del Pilar Sánchez-Camargo et al., 2018). The review further elaborates on emerging applications such as integration with supercritical water oxidation (SCWO) and the recovery of rare earth elements and plasticizers. These hybrid applications had been less thoroughly studied in earlier literature but are now gaining

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traction as viable industrial-scale solutions (Lyu et al., 2021). Thus, the review demonstrates that $scCO_2$ not only serves as a remediation tool but also as a resource recovery agent, contributing to waste valorization and circular economy principles.

The engineering challenges related to high-pressure equipment and scale-up of $scCO_2$ systems were consistently acknowledged in previous technical studies (del Pilar Sánchez-Camargo et al., 2018). The findings from 13 articles in this review reinforce those challenges while also offering solutions through improved equipment design and process modeling. Earlier studies had emphasized the necessity for corrosion-resistant materials and safety systems to manage pressure fluctuations and decompression risks (Liu et al., 2021). This review confirms those concerns and also highlights the adoption of computational fluid dynamics (CFD), finite element analysis (FEA), and thermodynamic modeling tools to optimize reactor design and ensure operational stability. The literature also discusses modular system configurations that support flexible scale-up strategies, a concept previously proposed but now validated through industry implementation. These advancements collectively address longstanding concerns about cost, safety, and scalability.

Industrial case studies serve as critical validations of $scCO_2$'s theoretical and experimental promise. Earlier reports mostly described laboratory results or small pilot-scale trials, leaving a gap in large-scale commercial application (Tobiszewski, 2019). This review fills that gap by presenting robust case studies from Nestlé, Pfizer, and BASF, each of which has successfully scaled and integrated $scCO_2$ into full-scale production. The Nestlé decaffeination process preserved organoleptic quality while achieving nearly complete caffeine removal, a result long hypothesized but now confirmed in practice. Pfizer's use of $scCO_2$ for solvent-free drug processing demonstrates that such systems are not only technically feasible but also compliant with global pharmaceutical regulations. BASF's adoption of $scCO_2$ in polymer coating operations confirms prior experimental findings and proves that solvent-free surface treatment is achievable without sacrificing performance. These industrial validations extend earlier hypotheses into proven operational models. Furthermore, this systematic review bridges the gap between laboratory-scale experimentation and industrial-scale implementation of $scCO_2$ technology. The reviewed findings not only support the results of earlier studies but also broaden the scope by including empirical evidence from commercial operations. The integration of $scCO_2$ into diverse sectors—including food, pharmaceuticals, materials, and environmental engineering—confirms its versatility and technological maturity. Prior limitations such as solubility constraints, equipment cost, and operational complexity are increasingly addressed through hybrid process designs, material innovations, and advanced modeling tools. As a result, $scCO_2$ stands validated not only as a green alternative to conventional solvents but also as a competitive industrial process driver across multiple sectors.

CONCLUSION

The comprehensive synthesis of 163 systematically reviewed studies confirms that supercritical carbon dioxide ($scCO_2$) serves as a versatile, efficient, and environmentally sustainable alternative to conventional solvents across a wide spectrum of industrial applications. Its unique physicochemical properties—including tunable density, low toxicity, and high diffusivity—enable high-performance extraction, purification, synthesis, and material processing with minimal environmental impact and compliance with stringent safety and regulatory standards. From the successful commercial-scale decaffeination by Nestlé to Pfizer's pharmaceutical particle design and BASF's solvent-free polymer coatings, $scCO_2$ has proven its industrial viability, operational scalability, and alignment with green chemistry principles. The technology's role in recovering high-value bioactives, enhancing reaction kinetics, treating hazardous waste, and modifying polymers underscores its interdisciplinary relevance and adaptability. Furthermore, engineering advancements in high-pressure equipment design, computational modeling, and safety integration have addressed earlier limitations related to scale-up and process control. Altogether, these findings position $scCO_2$ not only as a scientific innovation but also as a commercially adopted, forward-facing solution in modern sustainable manufacturing and environmental management.

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eISSN: 3067-0470
DOI: 10.63125/n6esv923

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