

Microfluidic supercritical CO₂ applications: Solvent extraction, nanoparticle synthesis, and chemical reaction

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Junyi Yang  and Peichun Amy Tsai^{a)} 

AFFILIATIONS

Department of Mechanical Engineering, University of Alberta, Edmonton, Alberta T6G 2R3, Canada

^{a)}Author to whom correspondence should be addressed: peichun.amy.tsai@ualberta.ca

ABSTRACT

Supercritical CO₂, known for its non-toxic, non-flammable and abundant properties, is well-perceived as a green alternative to hazardous organic solvents. It has attracted considerable interest in food, pharmaceuticals, chromatography, and catalysis fields. When supercritical CO₂ is integrated into microfluidic systems, it offers several advantages compared to conventional macro-scale supercritical reactors. These include optical transparency, small volume, rapid reaction, and precise manipulation of fluids, making microfluidics a versatile tool for process optimization and fundamental studies of extraction and reaction kinetics in supercritical CO₂ applications. Moreover, the small length scale of microfluidics allows for the production of uniform nanoparticles with reduced particle size, beneficial for nanomaterial synthesis. In this perspective, we review microfluidic investigations involving supercritical CO₂, with a particular focus on three primary applications, namely, solvent extraction, nanoparticle synthesis, and chemical reactions. We provide a summary of the experimental innovations, key mechanisms, and principle findings from these microfluidic studies, aiming to spark further interest. Finally, we conclude this review with some discussion on the future perspectives in this field.

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I. INTRODUCTION

A supercritical (sc) fluid represents an intriguing phase achieved when a substance exceeds its critical pressure and temperature.¹ These fluids, in the absence of surface tension for a supercritical phase, exhibit combined properties of high density (typically associated with a liquid state), low viscosity (similar to a gaseous state), and an intermediate diffusivity between the gas and liquid phases.² Compared to a liquid solvent, the higher diffusivity and lower viscosity of supercritical fluids enhance mass transfer, beneficial for the applications of extraction and chromatography.² Supercritical fluids also occur naturally under extreme pressure and temperature conditions, such as supercritical water near underwater volcanoes and supercritical carbon dioxide (CO₂) in the atmosphere of Venus.³ Among various supercritical fluids, supercritical CO₂ stands out for industrial applications due to its relatively low critical pressure and temperature ($P_c = 7.4$ MPa, $T_c = 304$ K),⁴ as opposed to other fluids like water ($P_c = 22.1$ MPa, $T_c = 467$ K)⁴ and ethanol ($P_c = 6.3$ MPa, $T_c = 514$ K).⁴ Figure 1 shows a thermodynamic phase diagram for CO₂ at various pressures and temperatures.

As a green solvent, supercritical CO₂ is particularly appealing in pharmaceuticals and food science to replace organic solvents for non-toxicity.^{5,6} Its distinct mass transfer characteristics have led to a diverse range of applications, including supercritical fluid chromatography,² fluid extraction,⁷⁻⁹ nano- and micro-particle formation,¹⁰ polymer impregnation and foaming,^{11,12} drying, cleaning, and chemical reactions.¹³ In established industrial applications, supercritical CO₂ is utilized in extraction processes, such as decaffeination from coffee and tea,¹⁴ and essential oil extraction from botanic species. By adjusting system pressure and temperature, the fluid properties of supercritical CO₂—including density, viscosity, and diffusivity—can be conveniently tuned to improve its solvent power. However, since CO₂ molecules are non-polar with a net-zero dipole moment due to their symmetrical and linear structure, it has poor solvent strength toward dissolving polar compounds.¹⁵ To overcome this limitation, polar co-solvents such as ethanol are often used to augment the solvent strength of supercritical CO₂. Due to strong molecular interactions, supercritical CO₂ also exhibits exceptional solubility for fluorocarbon and carbonyl-based materials.³

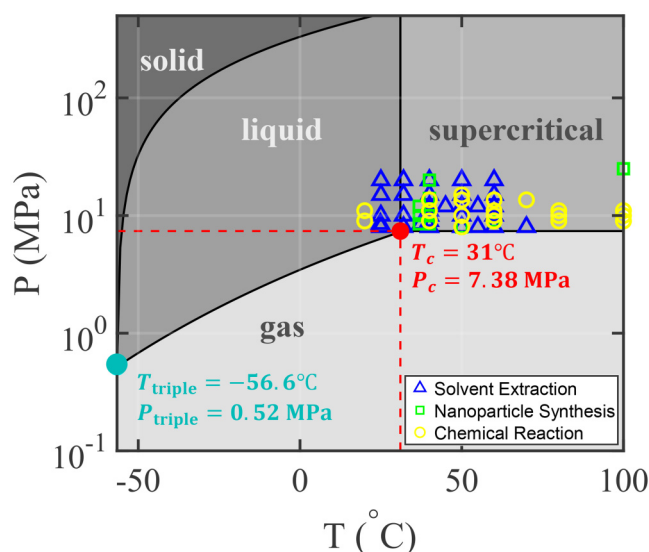


FIG. 1. A phase diagram for CO₂. CO₂ is in the supercritical state when the pressure and temperature exceed the critical values, P_c and T_c , respectively. The symbols on this phase diagram highlight the conditions for the key experimental investigations mentioned in this review. Here, we focus on reviewing the studies with applications of supercritical CO₂ in microfluidics, including solvent extraction, nanoparticle synthesis, and chemical reactions.

While supercritical fluid extraction (SFE) is typically performed in pressure vessels made of metal, rapid screening and process optimization are difficult using these macro-scale units.¹⁶ Microfluidics, when integrated with advanced imaging techniques, enables visualization of fluidic phenomena at a small scale. Microfluidics focuses on studying and controlling fluids within the length scale of 10^{-6} – 10^{-3} m.¹⁷ In microfluidic channel flow, the typical Reynolds number ($Re = \rho uL/\mu$, defined as the ratio of inertial to viscous forces, with fluid velocity u , density ρ , viscosity μ , and characteristic length scale L) ranges from 0.5 to 500,¹⁶ indicating predominantly laminar pipe flow due to miniaturization. In typical microfluidic channels, laminar flow results in slow diffusion-dominated fluid mixing, with minimal flow recirculation or turbulence.^{16,18} Consequently, to enhance fluid mixing, microfluidic designs often incorporate passive mixers (e.g., zigzag-shaped microchannels, geometric obstacles) or active mixers (e.g., pressure-driven flow with periodic perturbations).¹⁹ Recent experiments and numerical simulations have demonstrated that turbulent mixing can be achieved for supercritical fluids in microchannels under high pressure, making it advantageous for applications such as extraction, synthesis, and reaction.^{20,21} Another characteristic of microfluidics is the reduced mixing time (t_m) due to the small length scale ($t_m \sim l^2/D$), where l is the typical flow width and D is the diffusion coefficient.¹⁶ Moreover, for supercritical fluids in microfluidics, a narrower residence time distribution (RTD) exists due to the low viscosity of supercritical fluids and the reduced length scale of microfluidics.¹⁶ Residence time distribution (RTD) is a statistical distribution of the time that particles spend inside a

system, generally influenced by velocity profile and molecular diffusion.^{22,23} A narrower RTD is advantageous for nanomaterial synthesis, allowing for control over the size distribution of the nanoparticles.^{16,24} For an in-depth discussion of supercritical microfluidics fundamentals and applications, Marre *et al.* provide an extensive review.¹⁶

To explore the diverse applications of supercritical CO₂ in microfluidics, it is essential that the microfluidic chip can withstand a high fluid pressure exceeding 7.4 MPa. The thermodynamic condition of supercritical CO₂ in the microchannel is usually achieved and maintained by controlling the pressure and temperature above the critical condition. A high-pressure syringe pump injects compressed CO₂ into the microchannel, while a backpressure regulator downstream maintains the pressure above the critical condition.^{25–27} The temperature is kept above the critical point, either through electric heating^{28–30} or by immersing the microfluidic chip in a fluid bath.^{31,32} In addition to the challenges of maintaining the supercritical state in microfluidics, the fabrication of high-pressure microfluidics presents various challenges. Such microfluidic designs need to take into consideration factors including microchannel size, cross-sectional shape, spacing between individual channels, and packaging elements including interconnections and fittings, as well as thermal stress from heating.³³

Commonly, these devices are made of silicon and glass, which can endure pressure and temperature up to 25 MPa and 450 °C while maintaining good optical transparency for experimental observations.³³ Fabricating these “lab-on-a-chip” devices relies on photolithography, a technique originally developed for manufacturing integrated circuits in the 1950s. In this process, a desired pattern is transferred onto a thin layer of photoresist through UV exposure, followed by etching of the microchannels and subsequent bonding with a cover glass for enclosure.^{17,33} These fabricated microfluidic devices demonstrate resilience against elevated pressure and temperature while maintaining good optical transparency for visualizing fluid flow. In addition to silicon-glass microfluidic devices, recent developments in sapphire microreactors offer enhanced pressure and temperature resistance, with the microfluidic device capable of withstanding up to 50 MPa and 500 °C.^{34,35} This unlocks further potential for extraction, synthesis, chemical reactions, and other process engineering in “lab-on-a-chip” devices under more extreme conditions.

The optical transparency of microfluidics offers opportunities to obtain real-time information about the dissolution or reaction kinetics on the chip for supercritical CO₂ applications. For example, it allows for the observation of dissolution or extraction through size variations of fluid droplets.^{28–30,36–38} The thermodynamic properties, including the phase diagram, of supercritical CO₂ can be determined on a chip owing to the optical access provided by the microfluidics, making it a powerful tool for investigating various applications.^{39–41} Additionally, in a microfluidic device, local concentration changes can be visualized through color variation.^{42,43} *In situ* characterization, including fluorescent,^{44–46} ultraviolet-visible (UV-vis), and Raman spectroscopy,^{25,47,48} are useful tools for on-chip analysis of mass transfer and reactions. Integrating microfluidics with these *in situ* characterization techniques makes the investigation of supercritical CO₂ applications more convenient.

To date, many microfluidic investigations have been carried out for applications, including supercritical fluid extraction and nanoparticle synthesis with supercritical CO₂,^{36,42,49–54} encapsulation of microparticles for drug delivery,⁵⁵ screening flooding performance in

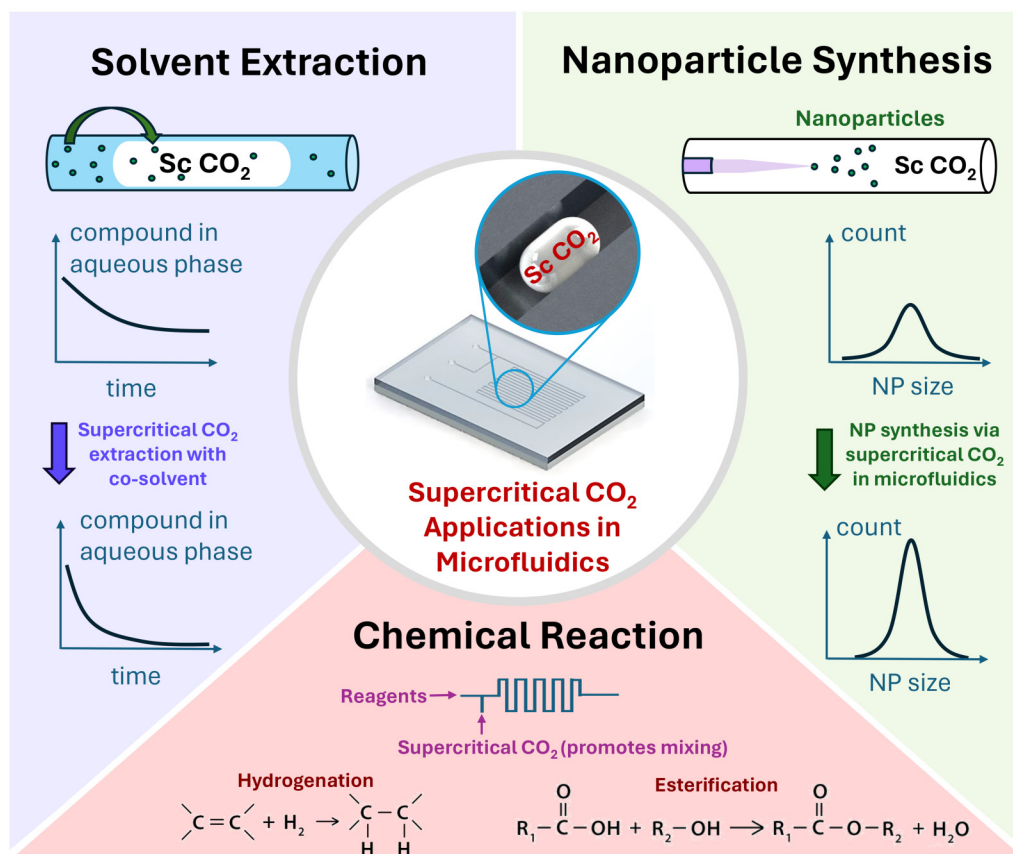


FIG. 2. Supercritical CO₂ applications in microfluidics, including solvent extraction, nanoparticle synthesis, and chemical reaction.

the oil and gas industry,^{56–58} CO₂ dissolution kinetics in an aqueous phase,^{25,28–30,38,44,59,60} and more. Compared with conventional methods, microfluidics allows precise manipulation of the fluid flow and enables superior control of parameters, such as the nanoparticle diameter and size distribution. In this perspective, we explore the current state-of-art in microfluidic studies for supercritical CO₂ applications, including solvent extraction, nanoparticle synthesis, and chemical reaction using supercritical CO₂ in microfluidics, as highlighted in Fig. 2. We aim to provide relevant background knowledge and highlight recent investigations concerning supercritical CO₂-related applications. We conclude by discussing the future perspectives and outlook of this field. For a comprehensive literature review on supercritical CO₂ applications in microfluidics, readers can be directed to Kazan.⁶¹

II. SOLVENT EXTRACTION USING SUPERCRITICAL CO₂ IN MICROFLUIDICS

A. Supercritical fluid extraction (SFE)

Solvent extraction is a separation process where a chemical compound is transferred from one phase to another immiscible

phase (usually from water to an organic solvent), driven by the solubility difference of the extracted compound in the two phases.⁶² Traditional liquid–liquid extraction involves using organic solvents, such as hexane, toluene, or dichloromethane. However, the heavy usage of these organic solvents poses threats to human health and the environment. For instance, inhalation of hydrocarbons such as toluene can be harmful, and chlorofluorocarbons (CFCs) contribute to the depletion of the atmospheric ozone layer.⁶³ Since the 1970s, when Zosel first patented supercritical CO₂ extraction of caffeine,¹⁴ the supercritical fluid extraction (SFE) technique has been gaining considerable attention due to their potential to replace hazardous organic solvents. Supercritical CO₂ effectively extracts valuable compounds from various raw materials, such as coffee beans, microalgae, hop, sesame, grape seeds, and many others.⁷ Furthermore, the compound separation upon CO₂ depressurization eliminates an additional purification step, which is typically required in conventional solvent extraction techniques. Nowadays, supercritical CO₂ extraction has already been employed in commercial processes for the decaffeination of tea and coffee. There is also a growing marketing demand for extracting high-value microalgae-derived products such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), astaxanthin,

TABLE I. Literature summary of solvent extraction using supercritical CO₂ in microfluidics.

Microfluidic design	Component extracted by CO ₂	Efficiency (%)	Pressure (MPa)	Temperature (°C)	Reference
Y-junction	Vanillin (V)	≈0	8–12	40–60	Assmann <i>et al.</i> ³²
	Methyl vanillate (MV)	5–17			
	5-Carbomethoxy-vanillin (5CV)	17–50			
	Methyl 5-carbomethoxy-vanillate (M-5CV)	27–66			
	Methyl dehydroabietate (MDHA)	80–100			
Parallel microchannels ^a Micromixer	Astaxanthin	11.9–98.6 ^b	8–20	40–70	Cheng <i>et al.</i> ⁴² Houng <i>et al.</i> ⁶⁵
	Gallic acid (GA)	≈0			
	Protocatechuic acid (PA)	≈0			
	Caffeic acid (CA)	≈0			
	Syringic acid (SA)	0–4.6			
	Ferulic acid (FA)	0–13.7			
	Benzoic acid (BA)	4–75.3			
	Ethyl acetate (EA) ^c	/			
Co-flow		/	8.5	24.85–37.35	Luther and Brauer ³⁷

^aMicrochannels were designed with trapping posts to trap algae cells for sc CO₂ extraction.

^b20 vol. % of ethanol or olive oil as a co-solvent significantly improved the extraction efficiency to >84%.

^cSupercritical CO₂ extraction of emulsion (SFEE), CO₂ acted as an anti-solvent in the process.

β-carotene and Lutein, for applications in the food, medicine, and cosmetic industries.^{8,64} The moderate critical temperature of CO₂ can avoid thermal degradation when extracting these bioactive compounds.

Table I provides an overview of recent microfluidic studies on supercritical CO₂ extraction. Supercritical CO₂ has been employed to extract a variety of compounds in microfluidics, with the extraction efficiency varying significantly across different species. The experimental conditions, including pressure, temperature, and co-solvent concentration, also play a crucial role in the extraction efficiency. For instance, supercritical CO₂ has been used to extract vanillin and other aromatic lignin oxidation products from a continuous aqueous phase in a segmented flow.^{31,32} The process is schematically illustrated in Fig. 3(a), where CO₂ extracts the valuable compounds that are initially dissolved in the continuous aqueous phase. As a result, the extraction efficiency was related to the polarity of the extracted compound. Among the five compounds, the less polar methyl dehydroabietate (MDHA) achieved nearly complete extraction, whereas the extraction of the more polar compound, vanillin, remained marginal regardless of pressure and temperature conditions.^{31,32} In addition, the extraction was improved under elevated pressure and reduced temperature conditions.^{31,32} In another study, various phenolic compounds have been extracted by supercritical CO₂ in microfluidics, including ferulic acid (FA), gallic acid (GA), protocatechuic acid (PA), caffeic acid (CA), syringic acid (SA), and benzoic acid (BA).^{65,66} Among these compounds, BA exhibited the highest extraction efficiency, reaching up to 75%, which increased with contact time, contact area, and CO₂ density.⁶⁵ Given the large variance in extraction efficiency among different compounds, this supercritical CO₂ extraction approach allows for selective extraction and separation.^{31,32}

In addition to supercritical CO₂ extraction in a segmented flow setting, researchers have also innovatively designed parallel structural traps in a silicon-glass microfluidic chip.^{42,67} These traps

can effectively immobilize the algae cells for supercritical CO₂ extraction, as seen in Fig. 3(b).^{42,67} The astaxanthin content was extracted by feeding a continuous stream of supercritical CO₂.⁴² Since astaxanthin is a lipid-soluble pigment, which naturally appears in red, the astaxanthin extraction efficiency was assessed by real-time monitoring of the color change in the cells.⁴² The results revealed a noticeable increase in the extraction efficiency from 12% to 63% when increasing the temperature from $T = 40$ to 70 °C.⁴² Moreover, by adding ethanol or olive oil as co-solvents, the extraction efficiency improved considerably from 22% (for pure CO₂ extraction) to as high as 98% at $T = 55$ °C, meanwhile significantly reducing the extraction time to within minutes.⁴² Astaxanthin has a much higher solubility in both ethanol and olive oil compared to supercritical CO₂, leading to more rapid extraction with the addition of co-solvents.⁴²

B. Supercritical fluid extraction of emulsion (SFEE)

Directly extracting the chemical compounds using supercritical CO₂, discussed above, sometimes results in low extraction efficiency limited by the solubility. Hence, supercritical fluid extraction of emulsion (SFEE) has been developed as an alternative approach, which utilizes CO₂ as an anti-solvent. As illustrated in Fig. 3(c), in the SFEE process, the target compound is initially dissolved in an organic solvent and dispersed in water to create an oil-in-water emulsion. Following this, supercritical CO₂ is introduced for solvent removal and the precipitation of nanoparticles in water. The agglomeration of nanoparticles can be avoided by adding surfactants into the system.⁶⁸ The SFEE method offers several advantages, including the reduction of organic solvent usage and allowing for a high load capacity of the extracted compounds. Ethyl acetate (EA) is most widely used as an organic solvent in SFEE, making the SFEE process quite flexible since EA can dissolve a broad spectrum of hydrophobic compounds.⁶⁸

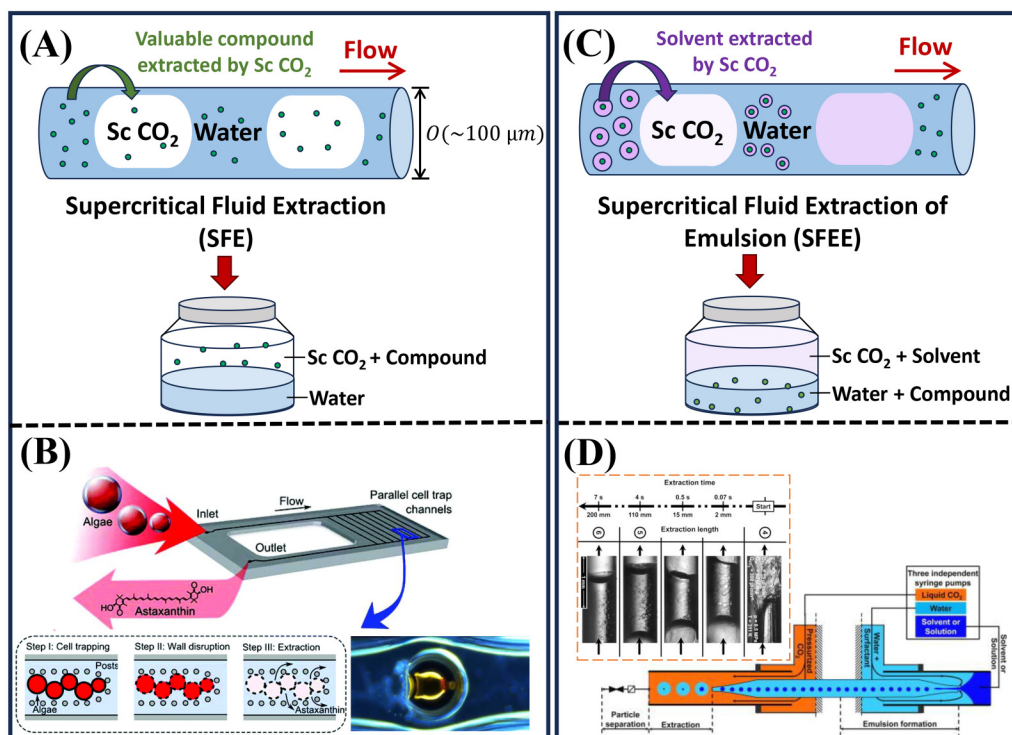


FIG. 3. Supercritical CO_2 extraction processes in microfluidics. (a) A schematic illustration of supercritical fluid extraction (SFE) in a microcapillary, where the valuable compound is extracted into the supercritical CO_2 bubbles. The typical microchannel diameter is of the order of a few hundred μm . (b) Supercritical CO_2 extracts astaxanthin from hydrothermally disrupted algae cells using a silicon-glass microfluidic device.^{42,57} Reproduced with permission from Cheng *et al.*, *Green Chem.* **19**, 106–111 (2017). Copyright 2017 Royal Society of Chemistry. Reproduced with permission from Cheng *et al.*, *Bioresour. Technol.* **250**, 481–485 (2018). Copyright 2018 Elsevier. (c) A schematic illustration of supercritical fluid extraction of emulsion (SFEE) in a microcapillary, where the supercritical CO_2 bubbles extract the solvent from the water/solvent/chemical compound mixture. (d) Supercritical CO_2 extracts an organic solvent, ethyl acetate, from water plus solvent emulsions in a microcapillary.³⁶ Reproduced with permission from Luther and Braeuer, *J. Supercrit. Fluids* **65**, 78–86 (2012). Copyright 2012 Elsevier.

Microfluidics can generate homogeneous emulsion with a well-defined droplet size by manipulating flow rate ratios,^{55,69,70} therefore being advantageous for investigating the SFEE process. Luther *et al.* studied the mass transfer in the SFEE process using fused silica capillaries with a co-flow geometry.^{36,37} Their experimental setup is shown in Fig. 3(d). In the first stage, an ethyl acetate (EA) in water emulsion was generated and stabilized with 1 wt. % of modified starch.^{36,37} In the second stage, EA was extracted from the emulsion by supercritical CO_2 .^{36,37} The process was visualized as supercritical CO_2 penetrated the water phase, causing the EA droplets to swell. Supercritical CO_2 penetration into the EA droplets led to a reduction in the refractive index of the droplets and made them invisible in water.^{36,37} Further downstream, the size of EA droplets reduced as they dissolved in supercritical CO_2 .³⁶ Although the authors presented a proof-of-concept study without any model compound dissolved in EA, the concept of utilizing supercritical CO_2 as an anti-solvent to extract organic solvents is versatile and can be extended to various applications, particularly in nanoparticle synthesis, discussed in Sec. III.

In this section, we review recent microfluidic studies on supercritical CO_2 extraction. The microfluidic platform serves as a

versatile screening tool for flow visualization and process optimization. Studying extraction at a smaller length scale using microfluidics greatly accelerates the investigation process, making it a good platform for initial studies. Nonetheless, it may face obstacles when scaling up to industrial-scale production. In these studies, supercritical CO_2 acts as either a solvent to extract valuable components or as an anti-solvent to remove unwanted organic solvents. The extraction efficiency is highly dependent on the polarity of the component³² and the addition of co-solvent (e.g., ethanol, olive oil).⁴² Extraction yield improves with increasing CO_2 density, which corresponds to higher pressure or lower temperature conditions.^{31,65} However, the extraction efficiency for many species remains low, and further research is needed to identify which components can be extracted most effectively.

III. NANOPARTICLE SYNTHESIS USING SUPERCRITICAL CO_2 IN MICROFLUIDICS

The utilization of nanoparticles in applications, including ceramic reinforcement and glass staining, dates back to ancient civilizations long preceding the scientific discovery starting from the

1980s.^{71,72} Today, organic and inorganic nanoparticles continue to play an important role in the field of electronics, catalysis, drug delivery, medical imaging, and so on. For example, carbon black serves as a common coloring and reinforcement additive in the production of rubber;⁷³ transition-metal nanoparticles function as efficient heterogeneous catalysts;^{49,74} and lipid or polymeric nanoparticles are effective drug carriers for drug delivery.⁷⁵ Nanoparticles exhibit unique size-dependent properties; their optical, electrical, or magnetic properties vary upon changing size and shape, which has sparked a growing interest in scientific research.⁷¹ The size and size distribution of nanoparticles are often determined via advanced characterization techniques such as atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) for dry nanoparticles, as well as dynamic light scattering (DLS) for nanoparticles in suspension.⁷⁶ In addition, zeta potential (ζ) measurements determine the surface charges of nanoparticles and indicate the stability of a colloidal nanoparticle suspension, where colloids with $|\zeta| > 30$ mV are stable and unlikely to aggregate.⁷⁷

Nanoparticle synthesis is classified into the “top-down” and “bottom-up” approaches, depending on whether the starting material is a bulk material or atoms/molecules.⁷⁸ The top-down approach reduces a bulk material to nanometer size mostly through physical processes, such as mechanical milling, laser ablation, sputtering, and ultrasonic dispersion. In contrast, the bottom-up approach involves the growth and agglomeration of seeding particles through processes, such as chemical vapor deposition, sol-gel method, and supercritical fluid synthesis.⁷⁸ Recently, there has been a rising demand for a green and sustainable synthetic route to replace organic solvents, by using environmentally benign solvents such as ionic liquid and supercritical fluid (most commonly, supercritical CO₂ and water).⁷⁹ As a bottom-up approach, synthesizing nanoparticles with supercritical CO₂ in microfluidics enables continuous production of nanoparticles and achieves superior size control and narrow size distribution.³³ Section III presents a literature review

on the current state-of-the-art in nanoparticle synthesis using supercritical CO₂ in microfluidic systems, with key information presented in Table II. We organize this section into subsections based on nanoparticle applications, including catalysis, semiconductor, nucleation and growth studies, and drug delivery.

A. Synthesis of metal nanoparticles for catalysis

Metallic nanoparticles, such as palladium (Pd) and nickel (Ni), have been widely used as heterogeneous catalysts in chemical reactions benefiting from their high surface-to-volume ratio, which leads to improved catalytic performance.^{74,82} Researchers have used a coaxial-flow microfluidic design for synthesizing Pd nanocrystals, a schematic of which has been illustrated in Fig. 4(a).⁴⁹ The inner flow consists of a mixture of Pd precursor/sc CO₂/H₂/toluene. As the fluid mixture contacted the outer flow consisting of ligands and toluene, the Pd-nanocrystals nucleated and were functionalized by different ligands.⁴⁹ The presence of supercritical CO₂ greatly enhanced the solubility of H₂ in toluene, thereby promoting the hydrogen reduction of the Pd precursor and successfully producing Pd-nanocrystals at 100 °C and 25 MPa.⁴⁹ The high-resolution transmission electron microscopy (HRTEM) showed a particle size distribution of 3.6 (± 0.6) nm, seen in Fig. 4(b).⁴⁹ The catalytic efficiency of the Pd-nanocrystals was evaluated in reactions involving boron compounds.⁴⁹ The resulting yield was highly dependent on the ligand attached to the nanoparticles, demonstrating that the functional group on Pd-nanocrystals needs to be tailored for targeted reactions.⁴⁹

B. Synthesis of semiconducting nanoparticles

The conjugated polymer has alternating single and double bonds in the carbon backbone chain, and its molecular structure induces high charge transport and semiconductive properties.⁸³ The organic semiconducting nanoparticles are light-weight, low-cost, and flexible, making them well-suited for applications in

TABLE II. Literature summary of nanoparticle synthesis using supercritical CO₂ in microfluidics.

Microfluidic design	Nanoparticle	Size (nm)	Pressure (MPa)	Temperature (°C)	Reference
Co-flow	Palladium (Pd) nanocrystal	3.6 ± 0.6	25	100	Gendrineau <i>et al.</i> ⁴⁹
Co-flow	Poly(3-hexylthiophene) (P3HT) nanoparticle	36 ± 8	10	40	Couto <i>et al.</i> ⁵⁰
		47 ± 12	8	50	
Co-flow	Tetraphenylethylene (TPE) nanoparticle	9 ± 3	10	40	Jaouhari <i>et al.</i> ⁸⁰
Co-flow	Fluorescent organic nanoparticle	16 ± 4	10	40	Jaouhari <i>et al.</i> ⁴⁶
T-junction	Polyvinyl alcohol (PVA) nanoparticle	10–20 ^a	8.5–12	36.85	Murakami and Shimoyama ⁵¹
T-junction	Ibuprofen/PVA nanoparticle ^b	231 ± 31	8.5–12	36.85	Murakami and Shimoyama ⁵²
T-junction	Timolol maleate (TM)-loaded liposome	80–3000 ^c	10	40	Murakami <i>et al.</i> ⁵⁴
T-junction	PEGylated liposome	270–417 ^d	10	40	Akiyama <i>et al.</i> ⁵³
T-junction	Stearic acid solid lipid nanoparticle	20–150 ^e	8.5–20	40	Wijakmatee <i>et al.</i> ⁸¹

^aDepending on the degree of PVA hydrolyzed.

^bIbuprofen/PVA nanoparticles were functionalized by chitosan.

^cDepending on the co-solvent (ethanol) flow rate.

^dDepending on the ratio of PEG:lipid.

^eDepending on the pressure and total flow rate of water and oil phases.

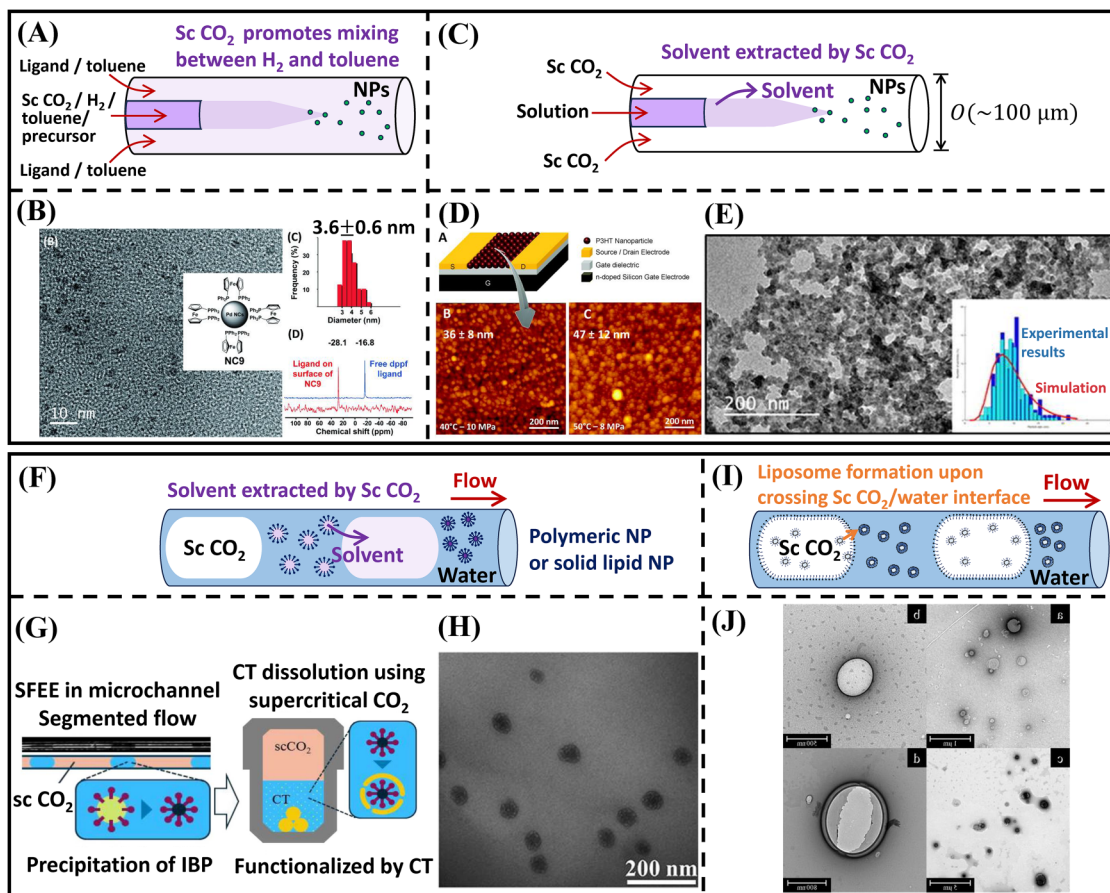


FIG. 4. Supercritical CO_2 -assisted nanoparticle synthesis in microfluidics. (a) Supercritical CO_2 enhances the mixing of H_2 and toluene, thereby promoting nanocrystal formation; the schematic is adapted from Ref. 49. Reproduced with permission from Gendrineau *et al.*, *Angew. Chem.* **124**, 8653–8656 (2012). Copyright 2012 John Wiley and Sons. (b) Palladium nanocrystal synthesis assisted by sc CO_2 in microfluidics as catalysts. The surface of palladium nanocrystals was functionalized by different ligands.⁴⁹ Reproduced with permission from Gendrineau *et al.*, *Angew. Chem.* **124**, 8653–8656 (2012). Copyright 2012 John Wiley and Sons. (c) Schematic illustration of nanoparticle formation in co-axial flow microfluidics, where supercritical CO_2 extracts the solvent and nanoparticles precipitate. (d) Sc CO_2 assisted synthesis of poly (3-hexylthiophene) nanoparticles in microfluidics for OFET applications.⁵⁰ Reproduced with permission from Couto *et al.*, *Chem. Commun.* **51**, 1008–1011 (2015). Copyright 2015 Royal Society of Chemistry. (e) Nucleation and growth of organic nanoparticles synthesized with sc CO_2 in microfluidics.⁸⁰ Reproduced with permission from Jaouhari *et al.*, *Chem. Eng. J.* **397**, 125333 (2020). Copyright 2020 Elsevier. (f) The process of supercritical fluid extraction of emulsion (SFEE) to fabricate polymeric nanoparticles of solid lipid nanoparticles for drug delivery applications. (g) Ibuprofen-loaded nanosuspension functionalized by chitosan produced using sc CO_2 in microfluidics.⁵² Reproduced with permission from Murakami and Shimoyama, *J. Supercrit. Fluids* **128**, 121–127 (2017). Copyright 2017 Elsevier. (h) Solid lipid nanoparticles of stearic acid generated in microfluidic flow using sc CO_2 .⁸¹ Reproduced with permission from Wijakmatee *et al.*, *Ind. Eng. Chem. Res.* **61**, 9274–9282 (2022). Copyright 2022 American Chemical Society. (i) Synthesis of liposomes in microfluidics using supercritical CO_2 . (j) TEM images of liposomes produced using sc CO_2 in a LipTube micro-mixing device.⁵⁴ Reproduced with permission from Murakami *et al.*, *Ind. Eng. Chem. Res.* **61**, 14598–14608 (2022). Copyright 2022 American Chemical Society.

photovoltaic cells, organic field-effect transistors (OFETs), and organic light-emitting diode (OLED). These semiconducting nanoparticles are prepared mostly through solution-based synthesis methods in a macroscopic batch process, sometimes leading to a broad size distribution.⁷⁷ Supercritical CO_2 has been used as an anti-solvent to fabricate semi-conducting organic poly (3-hexylthiophene) (P3HT) nanoparticles in microfluidics.⁵⁰ P3HT was first dissolved in an organic solvent, tetrahydrofuran (THF).⁵⁰ As shown in Fig. 4(c), P3HT solution in THF was injected as the inner jet in a co-flow microfluidic device, where supercritical CO_2

was introduced as the outer phase that extracted THF while P3HT nanoparticles precipitated.⁵⁰ Downstream of the microfluidic device, the system was depressurized, and the P3HT nanoparticles were directly spray-coated on an organic field-effect transistor (OFET) substrate, where the substrate and AFM images of the nanoparticle layer are seen in Fig. 4(d).⁵⁰ AFM measurements showed the P3HT nanoparticles were $36(\pm 8)$ nm when $T = 40^\circ\text{C}$, $P = 10$ MPa.⁵⁰ The transfer characteristic measurement (of the drain current vs the gate voltage) demonstrated a comparable performance compared to a classical deposition approach.⁵⁰

C. Nucleation and growth of organic nanoparticles

Despite many experimental efforts synthesizing nanoparticles using supercritical CO₂ in microfluidics, understanding the physics of nucleation and growth remains challenging, since the resolution of optical imaging systems is limited by light diffraction to a sub-micrometer scale. Jaouhari *et al.* investigated the precipitation of tetraphenylethylene (TPE) nanoparticles in THF using supercritical CO₂ as an antisolvent [see Fig. 4(e)].⁸⁰ Ultra-small TPE nanoparticles of size 9(±3) nm were generated in the microfluidics in a fast-mixing turbulent flow of $Re = 12\,000$.⁸⁰ Numerical simulation suggested that the characteristic mixing time between THF and supercritical CO₂ was crucial for the nanoparticle size and distribution.⁸⁰ For a turbulent flow in microfluidics, the mixing time was considerably reduced to 0.01 ms, comparable to the nucleation time, and resulted in small and uniform-sized nanoparticles.⁸⁰ Using a similar microfluidic setup, the authors extended their investigation to fluorescent organic nanoparticles and visualized the fluorescent intensity field near the mixing zone using a confocal microscope.⁴⁶ Similarly, homogeneous nucleation occurred due to fast mixing time computed from numerical simulation, resulting in an experimental nanoparticle size of 16(±4) nm.⁴⁶

D. Nanoparticle synthesis for drug delivery applications

Recently, supercritical CO₂ has emerged as a novel approach for synthesizing pharmaceutical nanoparticles in microfluidics, owing to its benign nature to the health and environment. The delivery of active pharmaceutical ingredients (APIs) is often limited by the low solubility of many drugs in water, as well as their instability in the colloidal system, ultimately leading to deficient bioactivity.⁸⁴ One effective method to improve drug loading is to use nanoparticles to encapsulate hydrophilic or hydrophobic drugs and form a suspension in water. The advancement of nanomedicine also provides opportunities for personalized precision medicine.⁸⁵ Nanomedicines approved by the US Food and Drug Administration (FDA) fell into three categories: lipid-based, polymeric, and inorganic nanoparticles.⁸⁵ In drug delivery applications, the nanoparticle size influences cellular uptake and drug transportation in the human body, and as a result, significantly affects therapeutic effectiveness.⁸⁶ A major concern in the conventional production of nanoparticles as drug carriers is the toxicity associated with the organic solvent residuals. To mitigate this, using supercritical CO₂ to fabricate nanoparticles in microfluidics has been investigated as an innovative approach for drug delivery applications.^{51–54,81} Microfluidics has demonstrated excellent control over fluid flow to encapsulate microparticles in emulsion droplets,^{55,87} hence exhibiting great potential for nanoparticle production in drug delivery applications. From Table II, the size of the synthesized nanoparticles was observed to vary based on experimental pressure, co-solvent flow rate, and the presence of surface functional groups.

One way to improve the drug loading is to encapsulate the API within a biocompatible and biodegradable polymeric carrier. Figure 4(f) conceptually illustrates a microfluidic approach to generate polyvinyl alcohol (PVA) nanoparticle suspension using the technique of supercritical fluid extraction of emulsion (SFEE). An

oil-in-water (O/W) emulsion was first prepared by mixing PVA, water, and an organic solvent [i.e., ethyl acetate (EA)], and it was subsequently injected into the microchannel as a continuous phase. Supercritical CO₂ forms a dispersed phase and extracts EA from the emulsion. In the experimental study by Murakami and Shimoyama, Sc CO₂ was able to extract EA completely when using 78%–82% hydrolyzed PVA.⁵¹ In a separate investigation, Murakami and Shimoyama loaded the EA/PVA/water emulsion with ibuprofen where the ibuprofen/PVA nanoparticles were further functionalized by chitosan (CT), as illustrated in Fig. 4(g).⁵² Chitosan has pH-dependent solubility and can rapidly dissolve in an acidic environment, facilitating a controlled release of the drug compounds.⁵² The aqueous PVA/CT/IBP nanoparticle suspension was able to achieve 0.3 wt. % ibuprofen concentration, which is 140 times higher than in its water-saturated solution, with an average particle size of 231(±31) nm from DLS analysis.⁵² This result demonstrates the superior drug loading capacity of nanoparticles synthesized via supercritical CO₂ in microfluidics.

Solid lipid nanoparticles emerged recently as a promising drug carrier due to their improved physical stability. The nanomedicine is immobilized inside a solid lipid core surrounded by a surfactant shell, forming a micellar structure.⁸⁶ As seen in Figs. 4(f) and 4(h), SFEE can be implemented to produce solid lipid nanoparticles. In comparison to the conventional solvent evaporation method, the microfluidic SFEE approach has been reported with reduced nanoparticle size and lower solvent residual.⁸¹ Interestingly, particle aggregation occurred in experiments at a pressure above 10 MPa, leading to a larger average nanoparticle size.⁸¹

In addition to polymeric and solid lipid nanoparticles, liposome is another type of drug carrier, which has been fabricated using supercritical CO₂ in microfluidics. A liposome, consisting of one or several lipid bilayers, serves as a nano-sized carrier for both hydrophilic and hydrophobic drugs.⁸⁶ The versatile structure of liposomes enables drug encapsulation by enclosing the hydrophilic compounds within the interior, or trapping the hydrophobic compounds inside the lipid bilayers.⁸⁶ The preparation of liposomes conventionally involves organic solvents such as ethanol, isopropanol (IPA) or EA. Figure 4(i) demonstrates the process of producing liposomes with supercritical CO₂ in microfluidics. The emulsions, which have a reverse micelle structure, are initially present in the CO₂ phase. As the emulsions are transported from CO₂ to water, they self-assemble into liposomes upon crossing the interface, as indicated by the arrow in Fig. 4(i). Murakami *et al.* utilized this microfluidic approach to produce liposomes loaded with a model compound—timolol maleate (TM).⁵⁴ The microfluidic approach achieved a remarkable size control of the liposomes, ranging from 80 to 3000 nm depending on the co-solvent flow rate, with the TEM images of the liposomes presented in Fig. 4(j).⁵⁴ The encapsulation efficiency of TM was as high as 70% when ethanol was used as the co-solvent with a flow rate above 0.2 ml min⁻¹.⁵⁴ Using a similar microfluidic method, liposomes could also be surface modified with poly-(ethylene glycol) (PEG) to form PEGylated liposomes.⁵³ PEG is a biocompatible and inert polymer, which protects liposomes during delivery and avoids severe immune response in the human body.⁵³ Zeta potential measurements confirmed the successful PEG coating of the liposomes, with the thickness of the polymer layer controlled by varying the PEG-lipid concentration.⁵³

In this part, we review several recent investigations on supercritical CO₂-assisted nanoparticle synthesis, with applications ranging from chemical catalysis to drug delivery. The microfluidic approach outperforms the conventional solvent evaporation method by synthesizing nanoparticles with reduced size, narrower size distribution, and lower solvent residuals.⁸¹ For pharmaceutical applications, in particular, the nano-sized drug carriers are outstanding in loading a high amount of active ingredients compared with the traditional approach, making it worthy of further investigation on the mechanisms of mass transfer.⁵² Additionally, the precise fluid manipulation offered by microfluidics enables surface modification of the nanoparticles, opening up opportunities for personalized nano-medicine in the future. Moreover, as noted in Table II, all experiments on supercritical CO₂-assisted nanoparticle synthesis were performed at a constant temperature, and the effect of temperature on nanoparticle size and distribution is yet to be explored.

IV. CHEMICAL REACTION USING SUPERCRITICAL CO₂ IN MICROREACTORS

Supercritical CO₂ has also been utilized in chemical reactions to eliminate the mass transfer barrier and intensify the reaction rate. In organic reactions such as hydrogenation and esterification, supercritical CO₂ often facilitates as a solvent medium for the reactants that are usually poorly soluble with one another. The reaction rate can be further enhanced through rapid mixing induced by the microfluidic design, compared to batch experiments using benchtop glassware.¹⁸ The small size of the microreactor has many merits when it comes to the field of organic synthesis; on the one hand, it promotes the contact between reactants due to the large surface-to-volume ratio, and on the other hand, it enables the safe handling of hazardous or explosive substances due to the small sample volume. Section IV summarizes the research efforts to utilize supercritical CO₂ in chemical reactions within microreactors, as summarized in Table III.

A. Hydrogenation reaction

Hydrogenation is an important reaction in the food and petrochemical industry, as it transforms unsaturated fat or hydrocarbon into saturated ones by adding hydrogen (H₂) and converting the double (or triple) bonds to single bonds. Heterogeneous catalysts, such as palladium (Pd), nickel (Ni), and platinum (Pt), are commonly used in hydrogenation reactions. The reaction rate of

heterogeneous hydrogenation is limited when using a conventional solvent, which is largely due to the low solubility of H₂ in these solvents.⁹³ Supercritical CO₂ has been discovered as an ideal solvent (or reaction medium) for hydrogenation reactions, as it forms a homogeneous phase with H₂ and removes the interphase mass transfer resistance.⁹³ Incorporating supercritical CO₂ with the hydrogenation in a microreactor is beneficial for creating efficient solid-liquid-gas contact.⁸⁸ Kobayashi *et al.* innovatively designed a microchannel covered by a thin layer of solid Pd catalyst immobilized on the channel wall.^{88,94} The reactants, H₂ and CO₂, were introduced to an external high-pressure cell and subsequently injected into the Pd-immobilized microchannel for reaction.⁸⁸ Six substances containing double or triple bonds were tested, where the double or triple bonds were reduced smoothly in the Pd-coated microchannel.⁸⁸ The reaction happened within 1 s with a yield rate higher than 90%.⁸⁸

Owing to the optical transparency of microfluidics, the hydrogenation reaction has also been visualized *in situ*, confirming that supercritical CO₂ creates an environment for rapid mixing between the reactants.⁸⁹ Trachsel *et al.* performed the hydrogenation of cyclohexene in a microreactor, where H₂ and cyclohexene were simultaneously introduced at the first T-junction as a segmented gas-liquid flow.⁸⁹ In the second T-junction, when CO₂ was introduced to the H₂-cyclohexene mixture, the phase boundaries vanished and the mixing was chaotic between H₂, cyclohexene, and CO₂ as a single phase, as seen in Fig. 5(a).⁸⁹ A higher reaction rate was observed as the temperature increased from 40 to 70 °C, whereas the change in reaction rate was insignificant with varying pressure.⁸⁹ Other than acting as a solvent, CO₂ itself can undergo hydrogenation to produce methanol as a source of fuel. Tidona *et al.* investigated supercritical CO₂ hydrogenation in a stainless-steel microcapillary, and the chemical reaction was carried out at ultra-high temperature of $T = 450$ °C and varying pressure of $P = 20$ –90 MPa.⁹⁰ CO₂ conversion rate was well below the equilibrium of the reaction network due to insufficient residence time for CO₂ conversion.⁹⁰ Same microreactor has also been incorporated with Raman spectroscopy to probe the phase behavior of CO₂ on-chip at different pressures and temperatures.⁴⁷

B. Esterification reaction

Esterification is a critical organic reaction to produce flavoring agents, fragrances, pharmaceuticals, and soaps.⁹⁵ It combines a carboxylic acid with alcohol to form an ester and water. Despite the

TABLE III. Literature summary of chemical reactions using supercritical CO₂ in microreactors.

Microfluidic design	Reaction	Pressure (MPa)	Temperature (°C)	Reference
Microreactor ^a	Hydrogenation of six substances	9	60	Kobayashi <i>et al.</i> ⁸⁸
Microreactor	Hydrogenation of cyclohexene	8–15	40–70	Trachsel <i>et al.</i> , 2009 ⁸⁹
Stainless-steel capillary	Hydrogenation of CO ₂ to methane	20–95	450	Tidona <i>et al.</i> ⁹⁰
Microreactor	Esterification of phthalic anhydride 1 + methanol	8–11	20–100	Benito-Lopez <i>et al.</i> ⁹¹
Microreactor	Esterification of oleic acid + methanol	10	60–120	Quitain <i>et al.</i> ⁹²

^aThe solid catalyst Pd was immobilized in the microchannel.

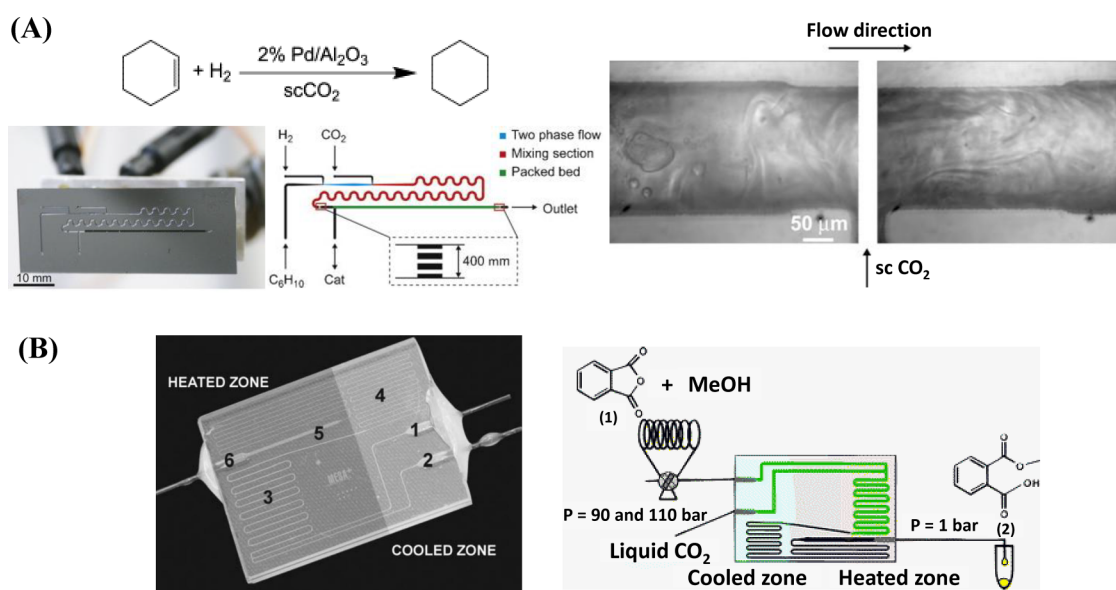


FIG. 5. Chemical reaction using sc CO₂ in microfluidics. (a) Hydrogenation reaction of cyclohexene in a silicon-glass microreactor with the addition of sc CO₂ as a solvent, where intensified mixing was observed upon sc CO₂ injection from the microscopic images on the right.⁴⁹ Reproduced with permission from Trachsel *et al.*, *J. Supercrit. Fluids* **48**, 146–153 (2009). Copyright 2009 Elsevier. (b) The glass microreactor and experimental setup were designed by Benito-Lopez *et al.* to perform an esterification reaction of phthalic anhydride and methanol, with sc CO₂ as a co-solvent that leads to rate enhancement.⁵¹ Reproduced with permission from Benito-Lopez *et al.*, *Lab Chip* **7**, 1345–1351 (2007). Copyright 2007 Royal Society of Chemistry.

significance of esterification reactions in a variety of commercial products, achieving a high conversion rate is still challenging due to the poor solubility between reactants and the slow reaction kinetics.⁹⁵ Benito-Lopez *et al.* first investigated the esterification reaction of phthalic anhydride 1 with methanol using a microreactor shown in Fig. 5(b).⁹¹ Adding supercritical CO₂ as co-solvent for the reaction reduces the viscosity of the supercritical CO₂–methane mixture and intensifies the reaction rate constants by O(∼100) compared to similar experimental conditions without the addition of CO₂.⁹¹ The second-order rate constants of the reaction were improved when increasing the temperature and pressure in microfluidics, compared to batch-size reactions at atmospheric pressure.⁹¹ The significant rate enhancement can be potentially attributed to a different reaction mechanism, where CO₂ induces the formation of localized clusters of the reactant molecules.⁹¹ Quitain *et al.* studied the reaction between methanol and oleic acid in a microreactor with supercritical CO₂ for biodiesel synthesis at $P = 8\text{--}12\text{ MPa}$ and $T = 60\text{--}120\text{ }^\circ\text{C}$.⁹² In this experimental study, supercritical CO₂ acts as a solvent for both reactants, as methanol and oleic acid are immiscible.⁹² The reaction product was oleic acid methyl ester (OAME), and the yield was determined by gas chromatographic analysis, where the reaction yield was found to increase with a higher temperature and a longer residence time in the microreactor.⁹² Furthermore, by recirculating the reaction products, the yield was found to improve significantly.⁹²

In this section, we review two organic reactions in microreactors, namely, hydrogenation and esterification, where supercritical CO₂ was used as a solvent medium for reactants that would

otherwise exhibit weak solubility in each other. Overall, it has been observed that supercritical CO₂-assisted chemical reactions significantly enhanced both hydrogenation and esterification processes, leading to higher reaction yields compared to batch reactions without supercritical CO₂. In the chemical reactions using supercritical CO₂, the reaction yield increased with a higher temperature and longer residence time in the microchannel. Given the safe handling (due to the small reagent volume) and rapid reaction, microfluidics provides an advantageous platform for visualizing fluid mixing and studying the reaction kinetics of supercritical CO₂-enhanced chemical reactions. However, it is unlikely that microfluidic reactors will replace batch-scale chemical reactors due to their low throughput currently.

V. CONCLUSION AND OUTLOOK

The adoption of supercritical CO₂ in microfluidics in applications has been a promising and ongoing field of research. This review highlighted three applications: solvent extraction, nanoparticle synthesis, and chemical reactions in pharmaceuticals, food science, chemical catalysis, and beyond. In these studies, microfluidics offers a convenient approach for flow visualization and process optimization. Despite these many advantages, several challenges could limit the advancement of supercritical CO₂ applications in microfluidics. These challenges include achieving the high pressure in microfluidics required to reach the supercritical state of CO₂. Additionally, fabricating silicon-glass chips in cleanroom facilities is an expensive process. From an extraction standpoint, although

supercritical CO₂ is an environmentally friendly solvent, its extraction efficiency can sometimes be low. For supercritical CO₂ extraction of high value-added compounds in microfluidics, it is challenging to transfer the relevant technologies from academic research to industrial-scale production in a profitable way. The microfluidic approach will likely remain a valuable tool for investigation due to its optical access and fast processing times. Furthermore, in the complex processes discussed in the review, there remains a lack of comprehensive understanding of nanoparticle nucleation and growth, supercritical CO₂ mass transfer mechanisms, and reaction kinetics. Without this fundamental knowledge, process optimization is challenging. Furthermore, scaling up the microfluidic process is essential for commercializing supercritical CO₂-assisted applications in microfluidics.

Supercritical CO₂ applications in microfluidics encompass interdisciplinary studies involving fluid dynamics, mass transfer, chemistry, and more. For future investigations, it would be beneficial to scale up the microfluidics from academic research to a commercialized solution. This could be accomplished through the use of parallel microfluidic channels or parallel microfluidic systems. Recently, numerical simulations have been performed to investigate the mixing performance when scaling up nanoparticle production using supercritical CO₂ in a microreactor from laboratory to industrial scale.⁹⁶ This novel approach opens up opportunities to predict and ensure sufficient mixing is achieved before scaling up the microreactor.⁹⁶ Numerical tools such as computational fluid dynamics (CFD) and machine learning are beneficial for predicting and optimizing mixing dynamics and production yield, which would attract more emphasis in future research on supercritical CO₂.^{96,97} Additionally, it would be valuable to systematically compare solvent residual, techno-economic performance, and the therapeutic effectiveness between the supercritical CO₂-assisted approach in microfluidics and the conventional solvent evaporation methods. To enhance the efficiency of supercritical CO₂ extraction, it is crucial to thoroughly understand the fluid mixing and mass transfer process associated with these applications. The effects of microfluidic design, supercritical CO₂ flow, and recirculation on nanoparticle nucleation and growth rates, as well as their size and distribution, are areas that require further investigation.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Junyi Yang: Visualization (equal); Writing – original draft (lead).
Peichun Amy Tsai: Conceptualization (lead); Funding acquisition (lead); Supervision (lead); Visualization (equal); Writing – review & editing (lead).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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