

Review

Some Advances in Supercritical Fluid Extraction for Fuels, Bio-Materials and Purification

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Abstract: Supercritical fluids are used for the extraction of desired ingredients from natural materials, but also for the removal of undesired and harmful ingredients. In this paper, the pertinent physical and chemical properties of supercritical water, methanol, ethanol, carbon dioxide, and their mixtures are provided. The methodologies used with supercritical fluid extraction are briefly dealt with. Advances in the application of supercritical extraction to fuels, the gaining of antioxidants and other useful items from biomass, the removal of undesired ingredients or contaminants, and the preparation of nanosized particles of drugs are described.

Keywords: supercritical water; supercritical methanol; supercritical ethanol; supercritical carbon dioxide; fuels; biomass; contaminant removal; drug particles

1. Introduction

Extraction by supercritical fluids pertains to the selective extraction of desired ingredients or removal of undesired ingredients from natural materials. The first aspect is illustrated by the gaining of hydrogen or biodiesel by supercritical water extraction of biomass on the one hand and the very large-scale application of supercritical carbon dioxide for the decaffeination of coffee on the other.

The supercritical fluids that have so far been used for the extraction purposes mentioned above include water, methanol, ethanol, and carbon dioxide, as well as their mixtures. It is necessary to know the relevant critical properties of these fluids, shown in Table 1, in order to appreciate the temperature and pressure conditions at which the supercritical fluid extractions have to be carried out. It is clear that much milder conditions are involved with the use of supercritical carbon dioxide than for the other supercritical fluids, but each fluid has its own particular advantages.

Table 1. The properties of pure water, methanol, ethanol, and carbon dioxide at the critical point.

Property	Water [1]	Methanol [2]	Ethanol [2]	CO ₂ [3]
Critical temperature, T_c /K	647.096	512.6	514.1	304.18
Critical temperature, t_c /°C	373.95	239.45	241.0	31.03
Critical pressure, P_c /MPa	22.064	8.092	6.137	7.38
Critical pressure, P_c /atm	217.75	79.86	60.57	72.83
Critical density, ρ_c /kg m ⁻³	322	272	276	468
Critical molar volume, V_c /cm ³ ·mol ⁻¹	55.95	117.7	166.8	94.0
Critical dynamic viscosity, η_C /μPa·s	24.5	40 ^a		29.2

^a Read from a small-scale figure in Reference [4].

The chemical and physicochemical properties of the supercritical fluids that are relevant to extraction are their hydrogen bond donation and acceptance abilities, and their polarity and polarizability. These properties for room temperature solvents are generally obtained by solvatochromic probes, and for the supercritical fluids they are discussed in Reference [5],

their applicability being much diminished. Hydrogen bonding and hydrogen bond donation and acceptance persist in supercritical water, methanol, and ethanol, but are absent in supercritical carbon dioxide that is non-polar but has an appreciable quadrupole moment. The dielectric permittivity of supercritical fluids is small and diminishes with increasing temperatures, but at a given temperature increases with the pressure, i.e., the density. Near the critical point the static permittivity $\epsilon_0 = 8.6$ for water [1], 4.8 for methanol [6], and 1.3 for carbon dioxide [7]. The cohesive energy densities and their square roots, i.e., the total (Hildebrand) solubility parameters, as well as the partial (Hansen) solubility parameters of the supercritical fluids are shown in Table 2 as near the reduced temperature $T_r = T/T_c = 1.1$ and pressure $P_r = P/P_c = 1.1$ as data are available.

Table 2. The cohesive energy densities ced , the total solubility parameters δ_H , and the partial solubility parameters for dispersion δ_d , for polarity δ_p , and for hydrogen bonding δ_{hb} of the supercritical fluids.

Condition and Property	Water [8]	Methanol [9]	Ethanol [10]	CO ₂ [11]
T/K	723	575	548	335
T_r	1.12	1.12	1.07	1.10
P/MPa	25	10	10	8
P_r	1.13	1.24	1.63	1.08
Ced/MPa	21	18	46	30
$\delta_H/MPa^{1/2}$	4.6	4.3	6.8	5.5
$\delta_d/MPa^{1/2}$	1.0	1.7	4.4	5.2
$\delta_p/MPa^{1/2}$	5.3	5.1	4.7	3.4
$\delta_{hb}/MPa^{1/2}$	2.6	4.3	2.1	3.9

The properties shown above pertain to the neat supercritical fluids dealt with in this review, but mixtures of these fluids are employed in many practical extraction processes. Therefore, some properties of such mixtures are also relevant for an appreciation of the advances made in this field. Thermophysical properties of mixtures of methanol and water at supercritical conditions are discussed in [12]. The critical temperatures and pressures of the mixtures depend, in a quadratic manner, on the mole fraction of the methanol:

$$T_c/K = 647.6 - 200.6 x_{MeOH} + 65.8 x_{MeOH}^2 \quad (1)$$

$$P_c/MPa = 22.06 - 23.58 x_{MeOH} + 9.34 x_{MeOH}^2 \quad (2)$$

A linear dependence of the critical densities and molar volumes of the mixtures on the mole fraction of the methanol is noted:

$$\rho_c/kg\ m^{-3} = 323.3 - 50.89 x_{MeOH} \quad (3)$$

$$V_c/cm^3\ mol^{-3} = 55.7 + 61.8 x_{MeOH} \quad (4)$$

Thermophysical properties of mixtures of ethanol and water at supercritical conditions are dealt with in Reference [13]. The critical temperatures and pressures of the mixtures depend in the following manner on the mole fraction of the ethanol $x = x_{EtOH}$:

$$T_c/K = 647.1(1 - x) + 514.1x + x(1 - x) [129.8 - 49.95(1 - 2x) + 4.834(1 - 2x)^2] \quad (5)$$

$$P_c/MPa = 22.06(1 - x) + 6.15x + x(1 - x) [-17.44 - 7.455(1 - 2x) - 2.701(1 - 2x)^2] \quad (6)$$

$$\rho_c/kg\ m^{-3} = 322(1 - x) + 276x + x(1 - x) [76.55 + 45.16(1 - 2x) + 115.71(1 - 2x)^2] \quad (7)$$

Only dilute solutions of water, methanol, and ethanol in supercritical carbon dioxide are relevant to the supercritical extraction processes, these polar co-solvents being called entrainers, since they enhance the ability of the non-polar carbon dioxide to dissolve polar solutes. The $T_c(P_c)$ curves of the

loci of the critical points of several co-solvent mixtures with supercritical carbon dioxide have been reported in Reference [14]. The solubility of methanol in supercritical carbon dioxide at 323 K increases from $x_{\text{MeOH}} = 0.0235$ at $P/\text{MPa} = 7.50$ through 0.0311 at $P/\text{MPa} = 8.77$ to 0.0540 at $P/\text{MPa} = 9.47$ [15]. The solubility of ethanol in supercritical carbon dioxide increases from $x_{\text{EtOH}} = 0.0331$ at 313 K and $P/\text{MPa} = 8.13$ to 0.0891 at 373 K and $P/\text{MPa} = 10.31$ [16]. The solubility of water in supercritical carbon dioxide is very small, being $x_{\text{H}_2\text{O}} = 0.00072$ at 0.39 K above T_c of the solvent [17], but water forms micro-emulsions at higher temperatures and pressures.

The methodology for the application of supercritical fluids has been advanced in recent years by using ultrasound and microwave assistance for the extraction process. Other techniques have been developed for obtaining the desired products from the extracts, namely rapid expansion of supercritical solvents (RESS), supercritical anti-solvents (SAS), and the gas saturated solutions method (PGSS) to produce nanoparticles of drugs for their enhanced administration and physiological availability. In these methods, the supercritical fluid is first used to extract the desired materials from natural sources and then application of these variants produces the required nano-particles. The rapid expansion of supercritical solvents (RESS) process was introduced by Matson et al. in 1987 [18], was fully described in Reference [19], and advances in the method were described in Reference [20]. The state-of-the-art supercritical anti-solvent (SAS) technique was described in Reference [21] and that of the gas saturated solutions method (PGSS) was described in Reference [22].

2. Supercritical Extraction Applied to Fuels

Advances in the desulfurization of coal by supercritical extraction with methanol and with ethanol have been noted. Supercritical methanol at 673 to 723 K removed about 45% of the organic sulfur from Canadian coal [23]. Desulfurization of low-ranking coal from Thailand appears to require the addition of potassium hydroxide to the supercritical ethanol. Up to 48% of the sulfur could be removed with 5 g dm^{-3} of KOH at 623 K and 8.3 MPa of supercritical ethanol [24].

The recovery of liquid fuels from coal by supercritical extraction has shown recent advances. Supercritical water for extraction of liquid products was applied to lignite coal of Turkish origin [25] and Dayan lignite coals [26]. Increasing pressure and temperatures in the range 673 to 723 K were effective for increasing the yield of liquid fuels, but higher temperatures enhanced mainly gas and light oil production. Supercritical water was also applied to some Chinese coals, the maximal extraction rate occurred near 670 K and the gas (CO , H_2 , CH_4) and extract yields increased with pressure [27]. Higher temperatures of 673 to 1033 K and pressures of 30 MPa were used for the supercritical extraction of brown coal from Russia, with a conversion of 48% to 63% to liquid and gaseous products [28].

Sub- and supercritical water extraction was applied to bitumen for the production of gaseous fuel, mainly hydrogen and carbon monoxide, at supercritical conditions [29]. Supercritical fluid extraction at 673 K with water (at 21.2–24.7 MPa), methanol (at 8.6 MPa), and ethanol (at 11.9 MPa), among other solvents, was applied to bituminous Illinois No. 6 coal, but the conversion yield to liquid and gaseous fuels with the water (34% and 39%) was larger than with methanol (8.4%) and ethanol (17.5%) [30]. Sensitivity to the pressure applied was noted for extraction with supercritical ethanol at 673 K; at 20.5 MPa it yielded a 35.7% conversion to liquid products, but only 78.6% ethanol recovery. At the expense of a much lower conversion to liquid products of 22.2% [31], the recovery was increased to 84.3% by lowering the pressure at 673 K to 12.7 MPa. Extraction by supercritical methanol and ethanol (also propanols, butanols, and pentanols) was applied to Brazilian coals with a recovery of >40% of liquid and gaseous products [32]. Pure ethanol as well as its aqueous mixtures (also isopropanol) were applied as supercritical fluids at 598–698 K and ≤ 12.5 MPa to high-ash Brazilian coal, for which increased temperatures and pressures increased the conversion yield [33]. Supercritical extraction with methanol and ethanol was applied to high-volatile bituminous coal from the Saar region in Germany and the dependence of the extraction yields on the conditions employed was studied [34]. Supercritical water with admixture in a 1:1 mass ratio of methanol and more so ethanol increased the yield of liquid products from coal significantly (at 623 K) [35].

Supercritical fluids also treated another kind of material, namely oil shales, in order to obtain liquid (eventually also gaseous) fuels. Extraction with supercritical methanol and its mixtures with water at 473 K of Green River oil shale showed that esterification products were responsible for a part of the methanol being consumed, but the process produced liquid organic materials beyond these products [36]. Some 90% of the organic material in the shale were obtained on extraction at 673 K with a 50 vol.% mixture of water and methanol for 34 min [37]. Chinese Maoming oil shales at 673 K were subjected to supercritical water with 45% oil recovery when heated at this temperature for 1 h [38]. When supercritical water was applied at a lower temperature, 648 K (just critical) to extract oil from Turkish oil shale, the yield was 75% after 1 h treatment [39]. Turkish (Bey pazari) oil shales were extracted with supercritical water up to 698 K, the asphaltene fraction diminished but the polar fraction of the produced oil increased in this temperature range [40]. Moroccan oil shales treated by supercritical water at 653 to 673 K yielded oils with increasing yields and diminishing fractions of asphaltenes [41]. Retorting and supercritical extraction with water at 712 K and 24.9 MPa of Jordanian (El-Lajjun) oil shales produced the highest oil yield at nearly 47% [42]. Russian oil shales (Bazhenov formation) were treated with supercritical water up to 753 K and liquid products were recovered at 673 K and 30 MPa, whereas at the highest temperature secondary hydrocarbon formation was observed [43]. The yield of liquid products from Russian (Krassava) and Bulgarian (Syssola) oil shales increased from 18 to 37 and 44% for the Russian shale, but less, from 13 to 18 and 35%, for the Bulgarian shale on admixture in a 1:1 mass ratio of methanol and more so ethanol to supercritical water (at 623 K) [35].

3. Supercritical Fluid Extraction from Bio-Materials

Recently, extraction with supercritical water, methanol, and ethanol of solutes from biomaterials has been extensively reported. However, the term 'supercritical fluid extraction' in the literature does generally pertain to extraction with supercritical carbon dioxide, possibly with modifiers, such as methanol and ethanol.

Extraction with supercritical water, methanol, and ethanol has been applied to cellulosic materials, including lignin. Treatment of Japanese Sugi wood (*Cryptomeria japonica*) with supercritical water resulted in various products that could be identified in the water-soluble, methanol-soluble, and methanol-insoluble fractions [44]. Japanese beech (*Fagus crenata* Blume) was treated with supercritical methanol containing some water, and a 10 vol% water at 623 K was found to be optimal, for obtaining products from the lignocelluloses [45]. Supercritical water at 653 K and 100 MPa was applied to Japanese beech as well as oil palm trunks to obtain low molecular size products [46]. German beech wood was treated with supercritical ethanol, optimally at 589 K, to produce bio-oil [47]. Pre-treatment by water at 453 to 623 K of holm oak was used to hydrolyze hemicellulose, and then supercritical water at 669 K at 24.5 MPa was used for extraction of low molecular mass products, e.g., lactic acid [48].

Cellulosic and lignin materials that were not of wood origin have also been subjected to supercritical fluid extraction in recent years. Bagasse of sugar cane stalks was treated by supercritical ethanol at 603 K to yield bio-oil [49]. Wet biomass (olive husk, cotton cocoon shell, and tea waste) can be dealt with directly by supercritical water without need of drying, to produce hydrogen and methane beside carbon oxides. The yields increase with temperature in the range 650 to 700 K and with pressure in the range 23 to 38 MPa [50]. The hydrolysis, fractionation, and extraction of biomass containing cellulose, hemicellulose, and lignin by supercritical water at 673 K was dealt with in two recent reviews [51,52]. The yields of phenolics, for example, increase with increasing density (pressure) and temperature of the supercritical water.

Extraction with supercritical carbon dioxide has been applied to non-wood cellulosic plant materials, such as leaves, roots, fruits, seeds, and pomace. Flavonoids have been extracted with supercritical carbon dioxide from *Scutellaria baicalensis* roots [53] and from *Maydis stigma* (from maize flowers) [54], and flavonoids as well as ginkgolides were extracted likewise from *Ginkgo* leaves [55]. Carotenoids were extracted with supercritical carbon dioxide from carrots with canola oil

as a co-solvent [56], from pitanga fruits (*Eugenia uniflora* L.) [57], and together with tocopherols and sitosterols from industrial tomato by-products [58]. Seeds of black sesame (*Sesamum indicum* L.) [59] and of fenugreek (*Trigonella foenum-graecum* L.) [60] were subjected to supercritical carbon dioxide extraction to obtain phytosterols and other bioactive ingredients. Peels of *Citrus Unshiu* were subjected to supercritical carbon dioxide extraction with an ethanol co-solvent entrainer to obtain nobiletin (a polymethoxyflavone) [61]. Carob biomass (*Ceratonia siliqua* L.) was extracted by supercritical carbon dioxide assisted by ultrasound to obtain phenolic antioxidants [62], which were also obtained by this technique from *Rumex acetosa* L. roots [63]. Extracts of Polish blackberry (*Rubus fruticosus*) pomace by supercritical carbon dioxide contained omega fatty acids, phytosterols, and tocopherols, and showed antioxidant activities [64]. Selective retrieval of phenolic compounds from guarana (*Paullinia cupana*) seeds was achieved by supercritical carbon dioxide extraction in Reference [65]. Algerian *Rosmarinus eriocalyx* was submitted to supercritical carbon dioxide extraction to obtain its antioxidant components [66]. Monocrotaline was extracted from *Crotalaria spectabilis* seeds by means of supercritical carbon dioxide with an ethanol co-solvent and the process was modelled in Reference [67].

Biodiesel, i.e., liquid fuel from biomass, and gaseous fuel were obtained from plant materials by supercritical fluid extraction with water, methanol, ethanol, and their mixtures. Supercritical water at 650 to 750 K and 23 to 48 MPa was used to produce hydrogen-rich gas from almond, hazelnut, walnut, sunflower shells, and cotton cocoon as wet biomass [68]. Supercritical fluid extraction with methanol and ethanol (also acetone and 2-butanol) was applied to bulrush plants, *Typha latifolia*, for liquefaction at 518 to 558 K [69]. Liquefaction to produce bio-oils by means of supercritical methanol or ethanol (also acetone) at 523 to 563 K was applied to thistle stalks, *Onopordum heteracanthum* [70]. Supercritical water at 923 K and 25 MPa was used for the gasification of glucose to produce hydrogen [71]. Flax seeds were subjected to supercritical ethanol extraction at 606 K for the production of bio-oils, consisting mainly of fatty acid esters [72].

Useful products were recovered from marine plants and algae when treated with supercritical fluids. Supercritical methanol at 528 K yields biodiesel from wet algae [73] and direct transesterification of algal biomass under supercritical methanol at 533 K and microwave irradiation was comparatively successful [74]. Supercritical ethanol yielded ethyl esters when wet algae are treated by it at 533 K and microwave irradiation [75]. Gasification of *Nannochloropsis gaditana* microalgae, producing mainly hydrogen, methane, and carbon dioxide, was affected by supercritical water at 24 MPa and 936 K [76]. The same microalgae as wet biomass were first subjected to hydrothermal liquefaction with subcritical water at 623 K and subsequently to extraction with supercritical water at 673 K in the presence of hydrogen gas to produce water-soluble biocrudes [77]. Supercritical carbon dioxide extraction of the microalgae *Nannochloropsis oculata* was used for the production of fatty acid methyl esters [78]. Brown seaweeds: *Saccharina japonica* and *Sargassum horneri*, are useful sources for oils extracted by supercritical carbon dioxide with ethanol co-solvent. One of the components of the extracted oils, fucoxanthin, has high anti-oxidant properties [79]. Colombian seaweeds (*Gracilaria mammillaris*) were extracted by supercritical carbon dioxide to obtain antioxidant bioactive substances [80].

4. Removal of Undesired Ingredients or Contaminants

The application of supercritical fluid extraction in the food industry is mainly by the use of supercritical carbon dioxide for the removal of undesired ingredients from food. The most widely known application is the decaffeination of coffee with supercritical carbon dioxide, this subject being most recently treated in Reference [81]. Less well known is the decaffeination of tea: green tea (*Camellia sinensis*) leaves contain many volatile components: various alcohols, terpenes, carbonyls, and nitrogen-containing compounds. On decaffeination with supercritical carbon dioxide the contents of these components are diminished along with that of the caffeine, which is detrimental to the taste and aroma of the tea beverage prepared from the leaves [82]. Near optimal conditions for the decaffeination of green tea leaves were determined in Reference [83]: supercritical carbon dioxide at 63 °C and 23 MPa with 3% ethanol co-solvent for 2 h, the caffeine yield being 96.6%, whereas that of

catechins (chlorophyll) removed being only 41%. Slightly more efficient for the decaffeination was a 7% ethanol content in the supercritical carbon dioxide at 70 °C and 30 MPa, where 97.4% of the caffeine was removed and only 38% of the catechins [84]. A process has been described, in which a powder of green tea leaves of particle sizes of 0.2 to 0.6 mm is treated with supercritical carbon dioxide containing 1% ethanol co-solvent at 80 °C and 30 MPa for 2 h. In this process 70% of the caffeine is removed whereas only 6% of the catechins are removed from the leaves, the remainder conferring on them a desirable taste [85].

Black tea leaves (the more oxidized variety of *Camellia sinensis* leaves) have also been the subject of decaffeination with supercritical carbon dioxide with somewhat wet ethanol (12.5% water) at 53 °C and 30 MPa. It was optimal, 99.8% of the caffeine but only 3.3% of the phenolics having been removed [86]. Lower pressure extraction conditions, namely 60 °C and 9 MPa, were recommended for maximal decaffeination but better retention of theaflavins, thearubigins, and catechins [87]. Practically 100% of the caffeine was removed by supercritical carbon dioxide containing 2.5% or 5% ethanol at 62.5 °C and 37.5 MPa in a more recent study [88].

The decaffeination with supercritical carbon dioxide of some other beverage ingredients has also been studied, for instance of cocoa powder [89]. Conditions were sought for effective caffeine removal (80%) but retention of the polyphenolic (85%) and theobromine (94%) ingredients conferring antioxidant properties. The best conditions were 45% water as the co-solvent (wetting the cocoa powder) and extraction at 70 °C and 30 MPa.

An important application of supercritical carbon dioxide is the sterilization and virus inactivation of contaminated raw materials of the food industry and of its products. Such a treatment can replace thermal pasteurization detrimental to heat-sensitive products. The review by Perrut [90] describes one technique that had been employed for this purpose: Rapid pressurization/depressurization enhanced by pretreatment by a pulse of electric field. This procedure causes cell membrane rupture in bacilli, e.g., *Escherichia coli* and *Staphylococcus aureus*. The effect of pressure cycling on the inactivation of *Escherichia coli* by supercritical carbon dioxide was further studied in Reference [91]. Spores are resistant to this treatment, however, *Penicillium oxalicum* spores could be eliminated from contaminated wheat grains by inclusion of water in the supercritical carbon dioxide [92]. A similar effect is obtained with water-modified supercritical carbon dioxide applied to fungal spore contaminated barley seeds [93]. A stronger co-solvent effect on microbial inactivation than that of water is obtained by the oxidizing power of peracetic acid, a treatment applied for the storage at ambient temperatures of shredded mozzarella-type cheese [94]. Sterilization of oil palm fruits for palm oil production with supercritical carbon dioxide dispensed with steam sterilization [95,96].

Supercritical water has been applied for the removal of toxic ingredients from industrial materials and from contaminated soils, with concomitant total oxidation to innocuous gases (the SCWO process). An example is the treatment of transformer oil contaminated with polychlorinated biphenyls (PCBs) in South America [97]. In this study 99.6% conversion of the total organic carbon (TOC) and reduction of the PCB level to below detection limit was achieved at 540 °C and 24 MPa with hydrogen peroxide as the oxidant. In the Korean study [98], oil samples were emulsified in water forming the feed for the supercritical water and oxygen-enriched air was used as the oxidant. The optimal temperature and pressure were 500 °C and 26.4 MPa, the destroying efficiency was >99.9% of the TOC and the measured dioxin in the environment of the plant was less than 15% of the Korean allowed limit.

The treatment and remediation of soils contaminated with PCBs and polycyclic aromatic hydrocarbons (PAHs) by SCWO processes is the subject of a large number of reports in the last decade. The treatment of PAH-contaminated soil from a decommissioned Swedish mine with supercritical water extraction coupled with SCWO was studied in Reference [99], resulting in 91% PAH destruction. In a subsequent paper [100], the authors achieved a considerably better destruction of the PAHs than initially reported, namely 97.0% to 99.9%, depending on the compound. Another two-stage remediation process for PCB-contaminated soils and sediments [101] involves extraction with supercritical carbon dioxide modified by methanol and subsequent SCWO treatment. The first stage operates at 50 °C and

12 MPa with 5 mol% methanol and the second stage operates at 500 °C and 25 MPa. SCWO treatment of contaminated soils and sediments was compared in Reference [102] with other available methods in terms of removal efficiency and costs and was found to be competitive.

5. Preparation of Nano-Sized Particles

Several processes through which drugs could be prepared for ready administration in the form of submicron particles by employing supercritical carbon dioxide have been reviewed [103]. These processes included the supercritical anti-solvent (SAS), the gas anti-solvent (GAS) or precipitation with compressed anti-solvent (PCA) methods, as well as particle formation using the rapid expansion of supercritical solvents (RESS) method. Even 15 years later, the use of supercritical solvents in general, and supercritical carbon dioxide in particular, in the pharmaceutical industry was still called 'nascent' and not deemed to be mature [104]. A further method for making drugs ready for administration that was described was encapsulation in host materials, such as chitosan or synthetic polymers. More recently, the importance of the particle sizes of the active pharmaceutical ingredient in a drug has been reviewed in Reference [105], where the production of micro- and nanoparticles by the RESS, SAS, and other techniques is described.

The supercritical anti-solvent process (SAS) for the precipitation of amoxicillin, the system investigated being carbon dioxide + *N*-methylpyrrolidone, is described in Reference [106]. The particle size (submicron) and particle size distribution of the precipitated amoxicillin were the criteria used for the selection of the optimal pressure and composition conditions. These criteria were also emphasized in the review [107] of the SAS, because they determine the rate of dissolution of poorly soluble drugs in aqueous bio-fluids, hence their bioavailability. Ampicillin and amoxicillin are the antibiotics specifically treated in this study, again with *N*-methylpyrrolidone solvent. Microparticles of glycyrrhizic acid (the active ingredient of licorice) were produced by the supercritical anti-solvent process (ethanol solvent and carbon dioxide anti-solvent) [108]. These particles showed enhanced dissolution in aqueous biofluids compared to the original drug.

The rapid expansion of the supercritical solutions (RESS) method has been used for the formation of bio-erodible polymeric (polylactic or polyglycolic acid) microparticles for the controlled delivery of drugs. A modification of the RESS method, consisting of expansion into a liquid solvent rather than into vacuum or air, ensures the production of nanoparticles [109]. Expansion of a solution of indomethacin in supercritical carbon dioxide into water produced submicron particles of this drug [110]. The solubility of phenytoin in pure supercritical carbon dioxide is too small for effective application of the RESS process for the production of nanoparticles of this drug. However, saturation of the supercritical carbon dioxide with menthol co-solvent (added as a solid, saturation mole fraction is 0.147 at 45 °C) solves this problem satisfactorily [111]. Naproxen is sufficiently soluble in supercritical carbon dioxide for the application of the RESS process, and it was found that expansion into an aqueous medium produces submicron particles that show improved dissolution behavior compared with the original material [112], with similar results also for ibuprofen.

Controlled drug delivery has been effectively provided by co-crystallization with other ingredients by the use of supercritical carbon dioxide. Co-crystallization with carboxylic acid amides or pyridine carboxylates is effective for making drugs more readily bio-available. This method, using supercritical carbon dioxide and the RESS and SAS processes has been reviewed in Reference [113]. An instance is the use of nicotinamide with the anti-inflammatory drug diflunisal in a 2:1 proportion, the drug thus precipitated from the ethanol solutions by supercritical carbon dioxide as the anti-solvent has an enhanced dissolution rate compared with pure diflunisal.

Controlled drug delivery has also been effectively provided by incorporation of the drugs in polymeric matrices produced in supercritical carbon dioxide. Polylactic acid microparticles have also been produced by the RESS process from supercritical carbon dioxide [114] for the incorporation of phytosterol. Co-polymers of polylactic and polyglycolic acids as microparticles incorporating indomethacin have been produced by a variant of the SAS method, namely, solution-enhanced

dispersion by supercritical fluids (SEDS) [115]. This polymeric matrix, incorporating the antitumor agent 5-fluorouracil, was produced by an SAS method from supercritical carbon dioxide too [116]. Low-cross-linked polymethacrylate matrices, produced from 2-(dimethyl-amino)ethyl methacrylate and incorporating ibuprofen, were produced in supercritical carbon dioxide and shown to have high loading of the drug and efficient controlled release [117]. Soft contact lenses (Hilafilcon B) were impregnated with the drug flurbiprofen in supercritical carbon dioxide for effective release of the drug [118]. A more detailed exposition of the method was subsequently reported by these authors [119]. A solid lipid matrix consisting of a mixture of hydrogenated castor oil and glyceryl monostearate has been imprinted with ketoprofen in supercritical carbon dioxide solvent, permitting the controlled release of the drug [120].

The advantages of using supercritical carbon dioxide for the production of controlled-release polymer drug composites were summarized in Reference [121], where the challenges remaining in the application of this method were also addressed. The application of supercritical carbon dioxide to the preparation of finely divided powders of macromolecular drugs, such as proteins, genes, and insulin, for inhalation is reviewed in Reference [122].

6. Conclusions

The application of supercritical fluid extraction with supercritical carbon dioxide was introduced for the decaffeination of coffee beans by Zosel in 1974 [123]. This process has matured since then to a major industrial process, but advances in supercritical fluid extraction have been extensive in recent years. Supercritical water, methanol, ethanol, and their mixtures have been added to the use of supercritical carbon dioxide as extracting agents. The engineering aspects of the use of high temperatures (except in the case of carbon dioxide) and pressures have been satisfactorily dealt with, so that supercritical fluid extraction has become a mature and readily controlled process. The supercritical solvents are 'green' in that they have no detrimental effects on the environment. The selectivity of supercritical fluid extraction, being tunable by the temperature and pressure employed as well as added entrainers, is used for the solubilization of the desired solutes in a matrix, as the solvating power, driven by the density, can be altered over a wide range. Compared to traditional organic liquids, the supercritical fluids have higher diffusivity and lower viscosity, providing a significantly improved mass transfer of solutes. Applications in food, cosmetic, pharmaceuticals, agriculture, and dairy industries and at pilot scale upgraded to the industrial set up are dealt with in Reference [124]. Recent applications of supercritical fluid extraction include: gaining of bio-diesel fuels, antioxidants, and other useful items from biomass, removal of undesired ingredients or contaminants, and the preparation of nanosized particles of drugs, showing that further developments of supercritical fluid extraction are to be expected. Vitamin E in polycaprolactone nanoparticles was continuously produced by supercritical fluid extraction of emulsions using a high-pressure packing column in countercurrent mode [125]. Applications of seaweed hydrocolloids as thickeners, stabilizers, coagulants, and salves in the food, pharmaceutical, and biotechnology industries produced by neoteric extraction methods, such as supercritical fluid extraction, are highlighted in Reference [126].

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