REVIEW

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Pharmaceutical applications of supercritical carbon dioxide

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The appearance of a supercritical state was already observed at the beginning of the 19th century. Nevertheless, the industrial extraction of plant and other natural materials started about twenty years ago with the decaffeination of coffee. Today carbon dioxide is the most common gas for supercritical fluid extraction in food and pharmaceutical industry. Since pure supercritical carbon dioxide is a lipophilic solvent, mixtures with organic solvents, especially alcohols, are used to increase the polarity of the extraction fluid; more polar compounds can be extracted in this way. The main fields of interest are the extraction of vegetable oils from plant material in analytical and preparative scale, the preparation of essential oils for food and cosmetic industry and the isolation of substances of pharmaceutical relevance. Progress in research was made by the precise measurement of phase equilibria data by means of different methods. Apart from extraction, supercritical fluid chromatography was introduced in the field of analytics, as well as micro- and nanoparticle formation using supercritical fluids as solvent or antisolvent. This review presents pharmaceutical relevant literature of the last twenty years with special emphasis on extraction of natural materials.

1. Introduction

Extraction of natural material using supercritical carbon dioxide is a separation method known since about 30 years. Compared with traditional extraction methods like solvent extraction it shows several advantages. The use of chlorinated hydrocarbons or other organic solvents in industrial extraction processes is intended to be reduced in order to avoid health hazards and to minimize cost of energy for solvent removal and recycling. Steam distillation of volatile compounds e.g. essential oils is as well an energy-intensive separation technique and high temperatures may cause thermal degradation of valuable constituents. Therefore supercritical carbon dioxide is a selective solvent for the production of solvent-free extracts and is gaining increasing importance in pharmaceutical industry, whereas in food technology it is already established. Beside supercritical fluid extraction (SFE) other applications have been developed. Supercritical fluid chromatography (SFC) has been derived from conventional liquid chromatography methods, mainly HPLC as a powerful and universal separation method in both analytical and preparative scale. During the last decade so called nanoparticles gained more and more interest due to their very small particle size, their high surface area and consequently their enhanced dissolution rate and bioavailability. For that purpose particle design by means of supercritical fluids offers a promising alternative. The authors want to give a comprehensive literature survey of supercritical fluid applications relevant for the pharmaceutical and nutrition sector. Special attention is turned to supercritical fluid extraction of plant material, particularly with carbon dioxide. Chromatography and particle design are summarized in some review articles.

2. Historical review

At the beginning of the 19th century Cagniard de la Tour observed the appearance of the supercritical state for the first time [1]. Hannay and Hogarth proved the solvent power of supercritical fluids in 1879 by dissolving inorganic salts in supercritical ethanol [2]. Since the 1930s separations with supercritical fluids were proposed and applied to the refinement of crude oil and the fractionation and purification of natural and synthetic oils. The extraction of plant material or other natural sources in industrial scale started about 20 years ago with the decaffeination of crude coffee beans and the extraction of hops. The production of flavours, fragrances and spices are as well realized in commercial scale by supercritical fluid extraction. A detailed review in SFE applications until the middle of the eighties is given by Stahl et al. [3]. In the last fifteen years the supercritical fluid extraction techniques have been rapidly extended to many different plant species, which results in a broad spectrum of data available in the literature.

3. Supercritical fluids

3.1. The supercritical state

The supercritical state is defined by temperature and pressure of a pure component that lie above the critical values ($T > T_c$; $p > p_c$) of the regarded component. In a p-T-diagram the critical point marks the end of the vapour-pressure line. Above the critical temperature a gas cannot be liquefied by increasing pressure. Physical properties (e. g. density, dielectric constant) of the component vary continuously from gaseous or liquid condition to supercritical condition, thus no phase boundary is observed (Figs. 1, 2). Supercritical fluids have properties similar to those of liquids or gases. The densities are in the order of magnitude of liquid solvents, whereas the viscosities are in the same range as those of gases. The low viscosity and comparatively high diffusion coefficients improve mass transfer from drug matrix to the solvent and accelerate extraction processes. The solvent capacity of a supercritical fluid is decisively determined by its density. It can be varied by changing temperature and pressure, with a much stronger influence of the latter one, particularly in direct vicinity of the critical point, the so called near-critical region (Fig. 2). The density increases with increasing pressure and decreasing temperature. Thus the solvent power of supercritical fluids can be easily adjusted by changing these two parameters. Brunner [4] gives an extensive overview of properties of supercritical fluids. Based on supercritical

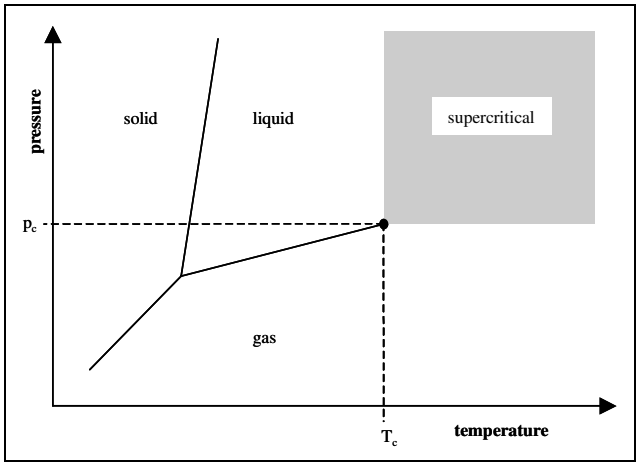

Fig. 1: p,T-Diagramm

fluid chromatography Smith has proposed definitions, as well as nomenclature and abbreviations according to IUPAC recommendations.

3.2. Supercritical carbon dioxide

Carbon dioxide is the most common solvent in supercritical fluid extraction, because of its superior properties compared to other gases or liquids. The critical temperature (31 °C) is rather low and the critical pressure (73.8 bar) is easy to realize as well. Further advantages are that carbon dioxide is not flammable or explosive, bacteriostatic, physiologically harmless, environmentally benign and easily available. The carbon dioxide molecule is totally symmetric so there is no dipole moment; this is the reason for its solvent power mainly for nonpolar or slightly polar substances.

3.3. Modifier effects – binary and ternary systems

To improve the solubility of polar solutes in the lipophilic solvent carbon dioxide, additional components may be applied. These more polar solvents are called modifier or entrainer and they are added in order to enhance the solvent power of the supercritical gas or to reduce the extraction pressure because of an increased solubility. Traditional solvents like alcohols (especially ethanol and methanol), chlorinated hydrocarbons, hexane, water or acetone are frequently used. These modifiers have volatilities between that of the solute and the supercritical fluid and boiling points between 20 and 100 °C. Phase equilibrium data for binary or ternary mixtures including carbon dioxide-methanol-(water) [6–10] and carbon dioxide-ethanol-(water) [11–13] are available. Mixtures of carbon dioxide with other modifiers (e.g. isopropanol, acetone) are as well described in the literature [15–18]. A general review about modified carbon dioxide including phase equilibria data is given by Page et al. [19].

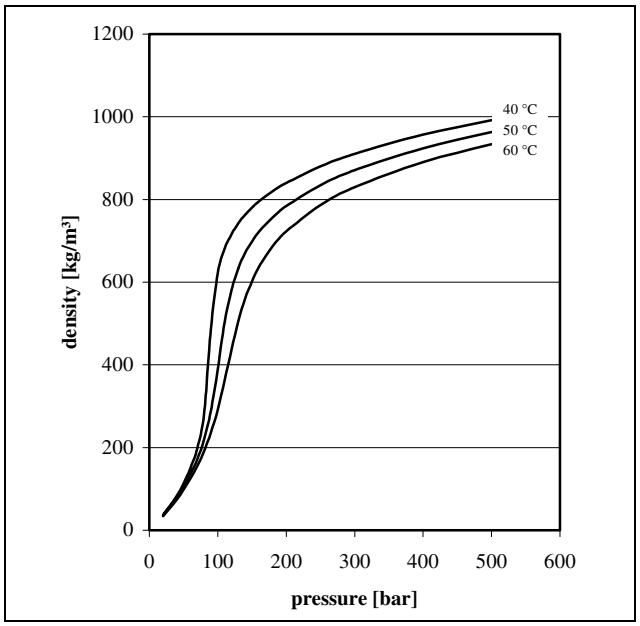

Fig. 2: Density of CO_2 as a function of pressure and temperature

4. Supercritical fluid extraction from plant material

Available literature about SFE covers a wide range of plant species, so different constituents have to be considered. Having a large survey of literature about supercritical fluid extraction within the last fifteen years, one can distinguish three main groups of constituents as targets for an extraction process. On a first level the three groups vegetable oil and related compounds, essential oil and other pharmacologically active compounds as well are divided. In a second step the scale of the extraction process is taken into account, analytical and preparative extraction processes are differentiated. The boundary was set in the range from 30 to 50 ml volume of the extraction vessel.
Analytical SFE is used predominantly as an alternative method for sample preparation in botanical and chemical analysis. Mostly the results are compared to conventional methods like soxhlet extraction or steam distillation. The intention of preparative scale SFE is to produce a commercial – ideally solvent free – extract for either food industry or as a basis for high valuable pharmaceutical formulations of medicinal plants. Until today such formulations usually contain solvent based extracts. If a technical- or pilot-scale SFE should be established first of all the feasibility of SFE for a specified separation problem has to be proven, considering also economic aspects. For countercurrent multistage separation processes Machado and Brunner describe a detailed process design methodology [20, 21]. For packed bed SFE from plant material it is done in a similar way by Lack and Marr [22]. Smith et al. and Reverchon and Osseo made a general energy analysis of supercritical fluid extraction processes [23, 24]. The latter examine three different flow schemes of process plants for the extraction of vegetable oil from soybeans considering particularly energy consumption.

4.1. Vegetable oils

4.1.1. Vegetable oils – analytical scale

Analytical scale supercritical fluid extraction is used as an alternative to conventional solvent extraction (e.g. soxhlet). Pure carbon dioxide is the most common extraction solvent but sometimes modifiers like hexane, ethanol, methanol or isopropanol are applied additionally. Various plants as well as algae, mushrooms and fish material are examined for their vegetable oil content by supercritical fluid extraction. A comparison to other methods for determination of vegetable oil content is given for *Brassica napus* [25, 26], *Glycine maximus* [26], *Helianthus annuus* [26] and *Lupinus luteus* [25]. Oils obtained by supercritical fluid extraction show the highest tocopherol but also the highest free fatty acids content. Fatty acids composi-

tion was determined in vegetable oils from *Gossypium spp.* [27], *Olea europaea* [28], *Oryza sativa* [29], *Rosa canina* [30], *Silybum marianum* [31] and *Solanum lycopersicum* [32], from the algae *Hypnea charoide* [33] and *Sargassum hemiphyllum* [34], the mushrooms *Pythium irregulare* [35] and *Saprolegnia parasitica* [36] and from the fish *Sardina pilchardus* [37]. Special attention was turned to the content of polyunsaturated fatty acids. *Rosa canina* [30] and *Silybum marianum* [31] were extracted with pure carbon dioxide, pure propane and a mixture of both solvents. Extractions from special matrices were carried out for the fractionation of vegetable oil from corn bran by carbon dioxide-ethanol mixtures [38] and for the extraction of phospholipids from egg yolk [39]. Enrichment and fractionation of polyunsaturated fatty acid esters from esterified fish oil was achieved by in line coupled supercritical fluid extraction and chromatography using ethanol modified carbon dioxide [40]. The selective removal of free fatty acids from seeds of *Nigella sativa* [41] and the modelling of oil recovery from the mackerel species *Scomber scombrus* [42] are further applications of analytical scale supercritical fluid extraction. Some models

Table 1: Vegetable oils – preparative scale

Plant	Targets	Gas	Conditions	Year	Ref.
Anacardium occidentale (cashew nut), shells	Composition of shell liquid, phenolic lipids, unsaturated fatty acids	CO_2	250 bar 40 °C	1991	[46]
Astrocaryum vulgare (tucuma palm), pulp	Extraction of carotenoid rich vegetable oil	CO_2	200–300 bar 40–70 °C	1999	[47]
Brassica napus (canola), oil seeds *Brassica campestris* (canola), flakes and meal	Recovery of vegetable oil; content of phospholipid, lecithin, tocopherol, sterols; solubility of canola seed oil	CO_2 + ethanol	208–668 bar 40–75 °C	1995 1998 1992	[48] [49] [50]
Carya illinoensis (pecan), halves	Palmitic, stearic, oleic, linoleic, linolenic acid in pecan oil	CO_2	413–668 bar 45–75 °C	1997	[51]
Corn, germ	Content of phospholipids; properties of protein residue	CO_2 + ethanol	300 bar 42 °C	1998	[52]
Egg yolk	Extraction and fractionation of lipids; fatty acids composition; kinetic studies and modelling; solubility data	CO_2 + methanol CO_2 + ethanol	150–360 bar 35–75 °C	1992 2001	[53] [54]
Elaeis guineensis (palm), fibers	Extraction of carotenoid and PUFA-rich oil	CO_2	200–300 bar 45/55 °C	1997	[55]
Fish oil ethyl esters	Fractionation of fatty acids ethyl esters	CO_2	145–195 bar 60–80 °C	1998	[56]
Glyceride mixtures (mono-, di-, triacylglycerol)	Fractionation	CO_2	172–344 bar 65–95 °C	1997	[57]
Glycine maximus (soy), seeds	Extraction of phospholipids, lecithins	CO_2 + ethanol	166–689 bar 60–80 °C	1999	[58]
Guilielma speciosa (pupunha), fruits	Fatty acids composition; modelling and kinetic studies	CO_2	250/300 bar 45/50 °C	2000	[59]
Helianthus annuus (sunflower), seeds	Extraction of vegetable oil; modelling and kinetic studies	CO_2	280 bar 40 °C	1997	[60]
Myristica fragrans (nutmeg), seeds	Simultaneous extraction of essential and vegetable oil	CO_2	90 bar 23 °C	1999	[61]
Oenothera biennis (evening primrose), seeds	Fractionation of triglycerides; fatty acids (PUFA) composition; solubility of vegetable oil	CO_2	200–700 bar 40–60 °C	1991 1998	[62] [63]
Olea europaea (olive), oil	Refining of olive oil: deacidification; content of stigmasta-3,5-diene	CO_2	260/310 bar 80/86 °C	1998	[64]
Panicum miliaceum (millet), bran	Fractional separation of vegetable oil kinetic studies	CO_2	300–500 bar 40–60 °C	2000	[65]
Prunus dulcis (almond), seeds	Extraction of vegetable oil; calory reduction of almonds; modelling and kinetic studies	CO_2	350/483 bar 40/60 °C	1993 1998	[66] [67]
Rosa rubiginosa (rose hip), seeds	Colour of vegetable oil; fatty acids composition; kinetic studies	CO_2	300–700 bar 40–80 °C	2000 2000	[68] [69]
Rubus chamaemorus (cloudberry), seed oil	Enrichment of carotenoids, tocopherols; recovery of PUFA-rich oil	CO_2	90–300 bar 40/60 °C	1997	[70]
Triticum vulgare (wheat), germ/gluten	Extraction/removal of vegetable oil; fatty acids composition; tocopherol content	CO_2	100–500 bar 10–65 °C	2000 2000	[71] [69]

Table 2: Essential oils – analytical scale

Plant	Targets	Gas	Conditions	Year	Ref.
Allium cepa (onion)	Concentration of sulphur in oleoresins	CO_2	150–450 bar 35–65 °C	1998	[72]
Archangelica officinalis (angelica), fruits	Angelica oil compounds (phellandrene, spathulenol); furanocoumarins	CO_2	80–140 bar 40–100 °C	1996	[73]
Baccharis dracunifolia (vassoura)	Vassoura oil composition (nerolidiol, spathulenol)	CO_2	90–120 bar 40–60 °C	2000	[74]
Boswellia thurifera (frankincense)	Oil composition in Chinese herbal medicines	CO_2	60–200 bar 50 °C	1991	[75]
Carum carvi (caraway), fruits	Caraway oil content (carvon, limonene) in consecutive extractions	CO_2	97 bar 50 °C	1994	[76]
Cellulose, spiked (model matrix)	Limonene, eugenol, caryophyllene, carvon, santonin	CO_2	50–250 bar −10–80 °C	1992	[77]
Chamomilla recutita (camomile), flowers	Composition of camomile oil	CO_2	250 bar 45 °C	1994	[78]
Cinnamomum cassia (cassia) *Cinnamomum ceylanicum* (cinnamon), bark	Cinnamon flavour compounds (coumarins, cinnamyl aldehyde)	CO_2 + acetonitrile CO_2 + tetrahydrofuran CO_2 + ethyl acetate CO_2 + methylbutylether	300 bar 70 °C static + dynamic	1995	[79]
Commiphora molmol (myrrh)	Oil composition in Chinese herbal medicines	CO_2	60–200 bar 50 °C	1991	[75]
Crocus sativus (saffron), stigmas	Determination of safranal content as well as its precursors	CO_2	100–300 bar 40–120 °C	2000	[80]
Curcuma longa (tumeric), rhizomes	Tumeric oil (turmerone, curcumene, citronellal); kinetic studies	CO_2	200–400 bar 40–60 °C	2000	[81]
Curcuma zedoaria	Oil composition (camphor, zederone)	CO_2	80–200 bar 50–100 °C	1995	[82]
Dragophalum moldavica (dragonhead)	Composition of peppermint oil (menthol, menthone); content of n-alkanes	CO_2 + acetone CO_2 + hexane CO_2 + dichlormethane	400 bar 70 °C	1993	[83]
Evodia rutaecarpaa	Oil composition in Chinese herbal medicines	CO_2	60–200 bar 50 °C	1991	[75]
Ferula galbaniflua (galbanum), latex	Galbanum oil (α-pinene, α-thujene)	CO_2 + methanol	90 bar 45 °C	1998	[84]
Ferulago nodosa	Volatile fraction (pinene, myrcene)	CO_2	91 bar 70 °C	1999	[85]
Humulus lupulus (hops), flowers	Enrichment of bitter principles (humulones, lupulones) and separation from essential oil	CO_2	0,2–0,9 g/ml 50 °C	1992	[86]
Illicum verum (star anise), fruits	Selective isolation of anethole	CO_2 + methanol	120 bar 80 °C	1996	[87]
Laurus nobilis (laurel), leaves	Composition of laurel leaf oil (cineole, terpinylacetate)	CO_2	80–150 bar 40/50 °C	2000	[88]
Lavandula angustifolia (lavender), flowers	Lavender oil (pinene, linalool); modelling and kinetic studies	CO_2	345 bar/50 °C 303 bar/50 °C	1994	[89]
Lavandula stoechas (Turkish lavender), flowers	Lavender oil (campher, fenchon)	CO_2	80–140 bar 35–50 °C	2000	[90]
Lemon oil-cyclodextrin complex powder	Determination of lemon oil (limonene, pinene)	CO_2	147–245 bar 30–60 °C	2000	[91]
Levisticum officinale (lovage), root, seeds, stems, leaves model plant matrix	Lovage oil (caryophyllene, limonene); mass transfer rate and coefficient; solubility data	CO_2	80–350 bar 10–55 °C	1998 1999	[92] [93]
Mentha piperita (peppermint), leaves	Composition peppermint oil (menthol, menthone, eucalyptol); content of n-alkanes/cuticular waxes	CO_2 (+ acetone) CO_2 + hexane CO_2 + dichlormethane	65–400 bar 25–70 °C	1993 1996 1999	[83] [94] [95]
Mentha pulegium (pennyroyal), blossoms and leaves	Aroma composition of pennyroyal (pulegeone, isopulegol)	CO_2	90–200 bar 40–50 °C	1998	[96]
Mentha spicata (spearmint), leaves	Spearmint oil (carvon, limonene)	CO_2 + ethanol	69–103 bar 39/49 °C	2000	[97]

Table 2 (continued)

Plant	Targets	Gas	Conditions	Year	Ref.
Origanum vulgare (wild marjoram), leaves *Pimpinella anisum* (anise), grain	Composition of marjoram oil (thymol, carvacrol); composition of anise oil (anethole)	CO_2	167 bar 55 °C	1990	[98]
Picea abies (spruce), needles *Pinus sylvestris* (pine), needles	Main constituents: spruce (pinene) and pine (cineol, camphor)	CO_2 + ethanol CO_2 + dichlormethane	300 bar 45 °C	1998	[99]
Piper nigrum (black pepper), seeds	Essential oil (caryophyllene, limonene, caren)	CO_2	150–300 bar 30–50 °C	1999	[100]
Rosmarinus officinalis (rosemary), leaves	Rosemary oil: pinene, camphor, limonene; modelling and kinetic studies	CO_2	100–345 bar 35–50 °C	1994 1997	[89] [101]
Sassafras albidum (sassafras), root bark	Safrole and related allylbenzenes (eugenol)	CO_2 + methanol	276–690 bar 50/80 °C	1994	[102]
Satureja hortensis (savory), leaves	Composition/fractionation of savory oil (carvacrol, terpinene, χ-terpinene); content of n-alkanes; study of antioxidant activity	CO_2 + acetone CO_2 + hexane CO_2 + dichlormethane	120–400 bar 40 °C–70 °C	1993 1999	[83] [103]
Syzygium aromaticum (clove), buds	Oil of cloves (eugenol, eugenylacetate, caryophyllene)	CO_2	200 bar 55 °C	1999	[104]
Tamarindus indica (tamarind), fruit pulp	Tamarind oil (aromadendrene, furfural, humulene)	CO_2	207 bar 50 °C	1994	[105]
Tanacetum parthenium (feverfew), flowers	Composition of feverfew oil (camphor, parthenolide)	CO_2	250 bar 45 °C	1994	[78]
Tanacetum vulgare (tansy), flowers	Composition of tansy oil (thujone)	CO_2	250 bar 45 °C	1994	[78]
Terpene mixture	Fractionation on silanized silica; modelling and phase equilibria data of various terpenes	CO_2	110–210 bar 37–57 °C	1998	[106]
Thymus zygis (thyme), blossoms and leaves	Aroma composition of thyme (thymol, geranyl acetate)	CO_2	90–200 bar 40–50 °C	1998	[96]
Zingiber officinalis (ginger), rhizome	Ginger oil (neral, geranial, zingiberene, bisabolene . . .); kinetic studies and modelling	CO_2	0,68–0,94 g/ml 245 bar 40 °C	1994 1996	[107] [108]

for the extraction of vegetable oils from plant matrices are described as an example for *Hippochae rhamnoides* [43], *Rosa canina* [44] and *Vitis vinifera* [45]. For further details about extraction models see chapter 6.

4.1.2. Vegetable oils – preparative scale

Lipids represent a complex chemical mixture consisting of mono-, di- and triglycerides as well as free fatty acids and some minor constituents. They are obtained from different groups of organisms like vegetables, fish, fungal or algae material. The recovery of high valuable vegetable oils has gained importance in the last few years. The pharmaceutical industry is mainly interested in polyunsaturated fatty acids (PUFAs) because of their beneficial pharmaceutical effects. Nutrition enriched in ω-3-fatty acids show antihypertensive and cardioprotective as well as anti-inflammatory effects. To improve the quality of those lipids a lot of refining steps are needed and supercritical fluid extraction is an alternative production method that is able to combine several steps under mild conditions. Supercritical fluid extraction with pure or modified carbon dioxide is not only applied for the recovery of oils but also for separation and fractionation of free fatty acids, for deodorization of vegetable oils and for delipidation of food products. The literature available on this topic is summarized in Table 1.

4.2. Essential oils

Essential oils for pharmaceutical use are volatile, strong smelling mixtures of lipophilic pure or oxygenated hydrocarbons; they are recovered from plant material. The conventional preparation methods are steam distillation, solvent extraction, enfleurage, maceration or cold expression, but SFE has proven to be most efficient. In contrast to steam distillation extracts produced by solvent or supercritical fluid extraction contain not only volatile but also a lot of other lipophilic constituents like sterols, waxes or colorants; those extracts are called oleoresins. Therefore sometimes refining procedures, fractional extraction or special separation techniques are necessary. Distinct essential oils mainly from *Citrus* species contain terpenes that do not contribute to the flavour or pharmacological effect but suffer from rapid oxidation or polymerisation. These are also reasons for fractional extraction or an additional deterpenation step using supercritical carbon dioxide.

Essential oils show cleansing, preservative, flavouring and mood elevating effects in cosmetics and perfumery products. They are pharmacologically used because of gastrointestinal effects as stomachics (*Citrus aurantium*, *Humulus lupulus*), as cholagogues (*Peumus boldus*, *Curcuma longa*) or carminatives (e.g. *Pimpinella anisum*, *Foeniculum vulgare*, *Carum carvi*). For the respiratory system extracts for example from *Pinus* species, *Picea* species, *Eucalyptus globulus*, *Thymus vulgaris* or *Salvia officinalis*

Table 3: Essential oils – preparative scale

Matrix	Targets	Gas	Conditions	Year	Ref.
Allium cepa (onion), bulbs	Onion oleoresin; sulphur content; fractional extraction	CO_2	100/300 bar 45/65 °C	1998	[109]
Angelica archangelica (angelica), root	Angelica root oil (pinene, phellandrene, cymene); content of coumarins	CO_2	80–400 bar 40 °C	1991 1998	[110] [111]
Anthriscus cerefolium (chervil), herb	Chervil oil (methylchavicol, allyldimethoxybenzene)	CO_2	300 bar 40 °C	1996	[112]
Apium graveolens (celery), herb and seeds	Oleoresins (triglycerides, essential oil, water) essential oil composition	CO_2	70–450 bar 20–55 °C	1996 1994	[113] [114]
Carum carvi (caraway), seeds	Caraway oil (carvone, limonene); modelling and kinetic studies	CO_2	75–300 bar 23–75 °C	1994 1999	[115] [116]
Carum opticum (ajowan), seeds	Essential oil composition of indian spices (pinene, limonene, thymol)	CO_2	80–450 bar 35–55 °C	1994	[114]
Chamomilla recutita (camomile), flowers, ligulate flowers	Camomile oil (apigenin, bisabolol, bisabolol-oxides, chamazulene); fractional extraction; modelling and kinetic studies; scale-up	CO_2 CO_2 + ethanol CO_2 + methanol CO_2 + propylene glycol	80–260 bar 40–80 °C	1990 2000 1994 1994 1995 1995 1997 1999	[117] [118] [119] [120] [121] [122] [123] [124]
Citrus aurantifolia (lime), peel oil	Fractional desorption from silica gel; deterpenation	CO_2	75–120 bar 40 °C	1997	[125]
Citrus aurantium (bitter orange), concrete	Orange oil; fractional separation; modelling	CO_2	80–100 bar 40 °C	1999	[126]
Citrus bergamia (bergamot), peel, peel oil	Bergamot oil (limonene, linalyl acetate) bergapten content; modelling and kinetic studies; fractional desorption from silica gel; deterpenation; phase equilibria data	CO_2	78–200 bar 40–80 °C	1999 1997 2000	[127] [128] [129]
Citrus medica (citrus), oil and peel + model mixture of limonene and linalool	Fractionation by pressure swing adsorption on silica gel; deterpenation of citrus oil; modelling, phase equilibria data of CO_2-limonene-linalool	CO_2	80–250 bar 40 °C–80 °C	1998 1996 1998	[130] [131] [132]
Citrus paradisi (grapefruit), flavedo	Grapefruit oil (limonene, cymene)	CO_2	80/250 bar 40 °C	1998	[133]
Citrus reticulata (mandarin), peel oil	Fractional desorption from silica gel; deterpenation	CO_2	75–120 bar 40 °C	1997	[125]
Citrus sinensis (orange), oil, peel, peel oil	Deterpenation of citrus oil; phase equilibria data of CO_2-limonene linalool; modelling and kinetic studies fractionated extraction	CO_2 CO_2 + hexane CO_2 + ethyl ether CO_2 + acetone	10–280 bar 20–75 °C	1997 1998 1996 1998 1999 2000 1999	[134] [135] [136] [137] [138] [139] [140]
Coleus aromaticus, leaves	Essential oil (terpinene, carvacrol)	CO_2	276 bar 60 °C	1996	[141]
Coriander sativum (coriander), fruits, seeds	Coriander oil (linalol, campher); cuticular waxes (n-alkanes), lipids; fractional separation	CO_2	150/250 bar 40/50 °C	1997 1996	[142] [113]
Cuminum cyminum (cumin), seeds	Essential oil composition of indian spices (pinene, limonene, thymol); cumin oil (pinene, terpinene)	CO_2	80–450 bar 35–55 °C	1994 1999	[113] [143]
Curcuma longa (tumeric), rhizomes	Tumeric oil (atlantona, tumerone, zingiberene); modelling and kinetic studies	CO_2 CO_2 + ethanol	250–300 bar 40/45 °C	2000 2000	[144] [145]
Cymbopogon citratus (lemon grass), leaves	Lemon grass oil; fractional extraction	CO_2 + hexane CO_2 + acetone CO_2 + methanol	81 bar 75 °C	1997	[146]

Table 3 (continued)

Matrix	Targets	Gas	Conditions	Year	Ref.
Eletaria cardamomum (cardamom), seeds	Cardamom oil (cineol, terpinylacetate)	CO_2	100–600 bar 40–60 °C	1991	[147]
Eucalyptus globulus (eucalyptus), leaves	Eucalyptus oil (pinene, cineole); fractional separation	CO_2	90 bar 50 °C	1999	[148]
Eugenia caryophyllata (clove), buds	Essential oil composition: eugenol, caryophyllene, eugenylacetat fractional separation	CO_2	80–120 bar 35–50 °C	1997 1998	[149] [150]
Eureka limon (lemon), peel oil	Fractional desorption from silica gel; deterpenation; elimination of psoralens, coumarins	CO_2	75–115 bar 40 °C	1994	[151]
Foeniculum vulgare (fennel), seeds	Fractional extraction of essential oil (fenchone, anethole) **and** vegetable oil; modelling and kinetic studies	CO_2	81–300 bar 40/50 °C	1999 1999	[152] [153]
Humulus lupulus (hop), cones and leaves	Hop oil (α-, β-acids, myrcene, caryophyllene, humulene)	CO_2	125–275 bar 40/60 °C	1990	[154]
Illicum verum (star anise), fruits	Essential oil (caryophyllene, eugenol, eugenylacetate)	CO_2	90 bar 50 °C	1998	[150]
Jasminum grandiflorum (jasmine), concrete and flowers	Jasmine oil (benzyl acetate, benzyl benzoate, linalool) fractional extraction and separation; effect of polar modifiers on extraction; modelling	CO_2 CO_2 + methanol CO_2 + acetone CO_2 + dimethyl-sulfoxide	80–200 bar 40 °C	1995 1992	[155] [156]
Lavandula angustifolia (lavender), flowers	Lavender oil (cineole, linalole, linalyl acetate); fractional separation; modelling	CO_2	90 bar 48 °C	1995	[157]
Lavandula intermedia (lavender), flowers	Lavender oil (linalol, linalylacetate); fractional extraction and separation	CO_2	80/300 bar 40 °C	1996	[158]
Lavandula officinalis (lavender) flowers	Essential oil (composition); fractional separation	CO_2	80–120 bar 35–50 °C	1997	[149]
Lavandula stoechas (lavender) flowers	Lavender oil (fenchone, campher)	CO_2	70–110 bar 30–50 °C	1994	[159]
Lippia alba, leaves	Essential oil (limonene, carvone)	CO_2	276 bar 60 °C	1997	[160]
Mentha pulegium (pennyroyal), flowers, leaves	Pennyroyal oil; modelling and kinetic studies; fractional separation	CO_2	100 bar 50 °C	2000 1999	[161] [162]
Mentha spicata (spearmint), leaves	Spearmint oil (piperitenone oxide, cineole)	CO_2	276 bar 60 °C	1999	[163]
Mentha x piperita (peppermint), leaves, stems	Peppermint oil (menthol, menthone, carvon, limonen); fractional separation	CO_2	60–180 bar 24–50 °C	1992 1994	[164] [165]
Milk fat	Flavouring compounds (lactones); modelling	CO_2	550–900 kg/m^3 45–75 °C	1990	[166]
Myristica fragrans (nutmeg), seeds	Simultaneous extraction of essential and vegetable oil	CO_2	90 bar 23 °C	1999	[61]
Ocimum basilicum (basil), leaves	Basil oil (linalool, methyleugenol); fractional extraction and separation modelling and kinetic studies; scale-up	CO_2	80–120 bar 35–50 °C	1994 1997	[167] [149]
Ocimum gratissimum (basil), leaves	Basil oil (thymol, carvacrol)	CO_2	276 bar 60 °C	1998	[168]
Origanum majorana (majoram), leaves	Majoram oil (cis-sabinene hydrat, cis-sabinene hydrat acetate); fractional separation; kinetic studies	CO_2	100 bar 50 °C	1992	[169]
Peumus boldus (boldo), leaves	Boldo oil; fractional extraction	CO_2 + hexane CO_2 + acetone CO_2 + methanol	75 °C 80 bar	1997	[170]
Pimenta dioica (pimento), leaves, berries	Pimento oil (cineol, eugenol, myrcene, caryophyllene)	CO_2	276 bar 60 °C	1997 1997	[171] [172]
Piper nigrum (black pepper), seeds	Oleoresins (piperine); modelling and kinetic studies	CO_2	280 bar 24–60 °C	1995	[173]

Table 3 (continued)

Matrix	Targets	Gas	Conditions	Year	Ref.
Rosa damascena (rose), concrete	Rose oil (phenylethanol, citronellol, phenylethyl acetate); fractional separation	CO_2	80–160 bar 40/45 °C	1996 1997	[174] [175]
Rosmarinus officinalis (rosemary), leaves	Rosemary oil; modelling	CO_2	100–160 bar 37/47 °C	1997	[176]
Salvia officinalis (sage), herb, leaves	Composition of oleoresins (triglycerides, sage essential oil, water); modelling and kinetic studies fractional separation	CO_2	90–250 bar 18–50 °C	1996 1995 1996	[113] [177] [178]
Salvia sclarea (clary sage), herb	Clary sage oil (sclareol)	CO_2	100 bar 40 °C	1999	[179]
Salvia triloba (three-lobed sage), leaves	Three-lobed sage oil (cineole, camphor)	CO_2	80 bar 40 °C	1999	[180]
Syzygium aromaticum (clove), bud	Clove bud oil (caryophyllene, eugenol, eugenyl-acetate); modelling and kinetic studies	CO_2	90–241 bar 35/50 °C	1995 1997	[181] [182]
Tagetes minuta	Essential oil (limonene, cis-ocimeme, dihydrotagetone, cis-ocimonene, trans anethol); fractional separation	CO_2	80 bar 40 ° C	1999	[183]
Tanacetum parthenium (feverfew), flowers	Feverfew oil (camphor, chrysanthenyl acetate, parthenolide)	CO_2	100–400 bar 40–60 °C	1999	[184]
Tangor murcote x *Citrus sinensis* (hybrid), peels	Essential oil; fractional extraction	CO_2 + hexane CO_2 + ethyl ether CO_2 + acetone	91 bar 60/75 °C static + dynamic	1998	[185]
Teucrium polium (germander), leaves, flowers	Germander oil (pinene, caryophyllene)	CO_2	100 bar 40 °C	1999	[186]
Thymus vulgaris (thyme), herb and leaves	Thyme oil (thymol, carvacrol); fractional extraction and separation; modelling	CO_2	80–400 bar 40 °C	1996 2000 2000	[158] [187] [188]
Vanilla planifolia (vanilla), beans	Vanilla oleoresin (vanillin, hydroxybenzaldehyde)	CO_2	100–130 bar 33–36 °C	1991	[189]
Zingiber officinalis (ginger), rhizome	Ginger oil (gingerol), oleoresins; selective extraction of pungent compounds or simultaneous extraction of aromatic compounds; fractional separation; kinetic studies	CO_2 CO_2 + ethanol	60–295 bar 0–80 °C	1995 1997 1998 1990 1997	[190] [191] [192] [193] [149]

are available in pharmaceutical formulations. Furthermore *Chamomilla recutita* is used as a spasmolytic and anti-inflammatory drug and eugenol gained from *Syzygium aromaticum* is applied as a preservative and antiseptic drug. A comprehensive overview of literature dealing with SFE of essential oils in analytical and preparative scale is given in Table 2 and Table 3, respectively.

4.3. Other pharmacologically active compounds

In Tables 4 and 5 plants or substances are summarized with a pharmacological principle that is neither due to their vegetable nor to their essential oil content. Thus a lot of different chemical structures with different physico-chemical properties are intended to be isolated. Whereas vegetable and essential oils are often lipophilic enough and therefore extractable with pure carbon dioxide, for those more polar components mainly in analytical scale a lot of different modifiers are added to the supercritical fluid. In preparative scale almost only pure or ethanol-modified carbon dioxide is used because of the non-toxic properties of these mixtures. Beside from active pharmacological extracts there are extracts, which serve as natural colourants, antioxidants or preservatives. Literature about SFE of these constituents is summarized in Table 4 for analytical scale and in Table 5 for preparative scale.

5. Supercritical fluid extraction from pharmaceutical preparations

Supercritical fluid extraction is emerging as a rapid, efficient and selective sample preparation method for routine analysis of active ingredients or excipients in pharmaceutical or cosmetic preparations. The extraction method offers the opportunity for on-line coupling with a chromatographic analysis-system like HPLC or GC/MS; a combination with supercritical fluid chromatography (SFC) is possible as well.

The content of preservatives, especially parabens, in cosmetics is interesting because of their potency to induce allergic contact dermatitis. The extraction from commercial creams, lotions or milks has been carried out using pure [291] or acetonitrile-modified [292] carbon dioxide. Anklam and Müller extracted vanillin as a flavouring compound from lozenges [293]. Furthermore SFE has been applied as a sample preparation method for the determination of active ingredients in solid formulations, e.g. for caffeine in analgesic tablets [293], megestrol acetate in

Table 4: Other pharmacologically active compounds – analytical scale

Plant/matrix	Target	Gas	Condition	Year	Ref.
Ancistrocladus korupensis, leaves	Anti-HIV-alkaloids (michellamine A and B)	CO_2 + methanol	455 bar 32–80 °C	1997	[194]
Apium graveolens (wild celery)	Phototoxic furanocoumarins (psoralen); effect of water content	CO_2	120–250 bar 35–80 °C	1997	[195]
Archangelica officinalis (garden angelica), fruits	Furanocoumarins (xanthotoxin, bergapten, imperatorin); fractional extraction	CO_2	80–500 bar 40–100 °C	1996 1996	[196] [73]
Artemisia annua, herb	Antimalaric sesquiterpenlactones (artemisinin and artemisinic acid)	CO_2 + methanol CO_2 + ethanol CO_2 + water CO_2 + toluol	150 bar 50 °C	1997 1997	[197] [198]
Bixa orellana (annatto), seeds pure bixin	Carotenoid pigments (bixin); solubility of bixin; natural food colourant (trans-bixin)	CO_2 + soybean oil CO_2 + ethanol CO_2 + chloroform CO_2 + acetonitril CO_2 + methanol	207–606 bar 40–80 °C	1991 1997	[199] [200]
Brosimum gaudichaudii, bark roots	Furanocoumarins (bergapten, psoralen); triterpenes (α-, β-amyrin)	CO_2	80 bar 60 °C	1993	[201]
Capsicum annuum (paprika)	Capsaicin and dihydrocapsaicin; natural food colourants (β-carotene); fractional extraction	CO_2 CO_2 + acetone, CO_2 + ethanol	140–600 bar 40/50 °C	1994 1999	[202] [203]
Cedrela toona (cedar), wood	Tetracyclic triterpenoids (cedrelone, a limonoid); modelling and kinetic studies	CO_2 + methanol	300/350 bar 40 °C	1996	[204]
Chlorella vulgaris, alga	Carotenoids, lipids	CO_2	200/350 bar 40/55 °C	1995	[205]
Coffea arabica (coffee), beans, soaked with water/unsoaked, brew of roasted coffee beans	Decaffeination rates; modelling of the extraction process; coffee aroma compounds	CO_2 + water CO_2	47–250 bar 40–80 °C	1992 1998	[206] [207]
Colchicum autumnale (meadow saffron), seeds	Colchicine	CO_2 + ether CO_2 + acetonitril CO_2 + ethanol CO_2 + acetone CO_2 + methanol	200–400 bar 40 °C	1999	[208]
Corn, spiked	Recovery of aflatoxins	CO_2	517 bar 65 °C	1996	[209]
Crotalaria spectabilis, seeds	Fractionation of pyrrolizidine alkaloids (monocrotalines) and lipids; solubility data in the cross-over region	CO_2 + ethanol	100–275 bar 35–55 °C	1988	[210]
Curcuma longa (tumeric), rhizomes	Extractability of curcumin; spectrophotometric measurements	CO_2 + ethanol	180–240 bar 40 °C	2000	[211]
Daucus carota (carrots); carrots and press cake	Antioxidant vitamins (α-, β-carotene); kinetic studies and diffusion models	CO_2 + ethanol CO_2 + methanol CO_2 + chloroform N_2O	303–606 bar 30–70 °C	1995 1997 1998 1996	[212] [213] [214] [215]
Digitalis lanata (foxglove), leaves	Cardiac glycosides (digoxin, acetyldigoxin, digitoxin, gitoxin)	CO_2 + methanol HFKW134a + methanol Fluoroform + methanol	380/404 bar 40–100 °C	1996 1997	[216] [217]
Dilophus ligulatus, algae material	Colour of extracts; antifungal compounds fractional extraction	CO_2	80–280 bar 35–55 °C	1991 1991	[218] [219]
Dioscorea nipponica, tuber	Diosgenin	CO_2	132–217 bar 33–60 °C	1995	[220]
Dorstenia bryoniifolia, rhizomes	Furanocoumarins (bergapten, psoralen); triterpenes (α-, β-amyrin)	CO_2	80 bar 60 °C	1993	[201]
Erythroxylum coca (coca), leaves	Cocaine; kinetic studies	CO_2 + methanol + water	150–250 bar 40–100 °C	2000	[221]
Eucalyptus globulus (eucalyptus), wood	Lipids (sterols, squalene, fatty acids)	CO_2 + methanol	100–250 bar 40–75 °C	2000	[222]

Table 4 (continued)

Plant/matrix	Target	Gas	Condition	Year	Ref.
Ginkgo biloba (maidenhair tree), extracts from leaves and fruits; standardized extract solutions and phytopharmaceuticals	Fractional extraction of fatty acids and ginkgolic acids; ginkgolides and bilobalide	CO_2 CO_2 + methanol CO_2 + ethyl acetate	110–339 bar 45/55 °C	1993 1996	[223] [224]
Glycine maximus (soy) products: miso, tofu, soy flour, soy meal	Anti-carcinogenic isoflavones (daizein, genistein)	CO_2 + methanol, CO_2 + chloroform	405–608 bar 50 °C	1996	[225]
Ilex paraguarensis (mate), leaves	Purine alkaloids (caffeine, theophylline, theobromine); solubility studies	CO_2	255 bar 70 °C	1999	[226]
Ipomoea batatas (sweet potatoes), root	Carotenoids (β-carotene)	CO_2	138–414 bar 38–48 °C	1993	[227]
Maclura pomifera (osage orange), root bark	Flavanones and xanthones (the latter with cytotoxic, antitumor activity)	CO_2 + methanol	405 bar 40–100 °C	1999	[228]
Magnolia officinalis (magnolia), bark	Neolignans (magnolol, honokiol) for the treatment of abdominal distension	CO_2 + methanol	245 bar 40/60 °C	1998	[229]
Magnolia virginiana (magnolia), flowers	Neolignans (methoxyhonokiol, magnolol, biphenyl ether)	CO_2 + methanol, CO_2 + chloroform	405 bar 40 °C	1995	[230]
Nicotiana tabacum (tabacco), leaves	Nicotine; dynamic modelling and kinetic studies	CO_2 + methanol	200/300 bar 50 °C	1996	[231]
Olea europaea (olive), leaves	Natural antioxidants (phenolic compounds)	CO_2 + methanol	155–334 bar 80–120 °C	1998	[232]
Oryza sativum (rice), bran	Extraction of oryzanol	CO_2	689 bar 30–75 °C	2000	[233]
Paeonia suffruticosa, cortex	Deoxyschisandrin, paeonol; kinetic studies	CO_2 + methanol	250 bar 40/60 °C	2000	[242]
Passiflora edulis (passion fruit), leaves	Glycosylated flavonoids	CO_2 + methanol CO_2 + ethanol CO_2 + ethyl acetate CO_2 + chloroform	101 bar 70 °C	1997	[234]
Paulinia cupana (guarana), seeds (45% water)	Caffeine; modelling of caffeine solubility and extraction rate	CO_2	136–272 bar 35–55 °C	1996	[235]
Piper methysticum (kava), root	Kava lactones (kavain, methysticin); fractional extraction	CO_2 + ethanol	250–450 bar 60 °C	1997 1999	[236] [237]
Rosmarinus officinalis (rosemary), extracts and leaves	Deodorizing of antioxidant rosemary extracts (carnosic acid, carnosol)	CO_2 CO_2 + ethanol CO_2 + water CO_2 + acetic acid CO_2 + extraction solvent	100–383 bar 40–120 °C	1998 1997	[238] [239]
Salvia miltiorrhiza bunge (tan-shen), root	Tanshinone IIA	CO_2 + methanol	100–250 bar 60 °C	1998	[240]
Schisandra chinensis, fruits, leaves, stems, seeds	Lignans (schisandrols, schisandrins) that improve liver function; kinetic studies; effect of plant matrix	CO_2 CO_2 + methanol CO_2 + ethanol	136–400 bar 40–80 °C	1998 2000 1999 1997	[241] [242] [243] [244]
Scopolia japonica, herb and roots Scopolamine and hyoscyamine pure substances	Tropane alkaloids (hyoscyamine, scopolamine); extraction of alkaloid-salts using basified modifiers	CO_2 + diethylamine/ methanol or diethylamine/water	102–340 bar 60 °C	1999	[245]
Scutellaria baicalensis, roots, soaked with ethanol	Flavonoids (baicalein, baicalin, wogonin) used in Chinese medicine	CO_2 + ethanol CO_2 + methanol CO_2 + water	197–400 bar 40–70 °C	1996 1999	[246] [247]
Senecio inaequidens *Senecio cordatus* (groundsel)	Pyrrolizidine alkaloids (senecionine, seneciphylline)	CO_2 + methanol	100/150 bar 50–60 °C	1991	[248]
Solanum lycopersicum (tomatoes)	Isolation of natural dyes (lycopene and β-carotene)	CO_2 + hexane CO_2 + chloroform	172–275 bar 40–80 °C	2000	[249]
Tamarindus indica (tamarind), seed coat	Natural antioxidants	CO_2 + ethanol	100–300 bar 40–80 °C	1995	[250]

Table 4 (continued)

Plant/matrix	Target	Gas	Condition	Year	Ref.
Taxus baccata *Taxus brevifolia* (yew), needles, bark	Anti-cancer taxanes (taxol, taxicin); kinetic studies	CO_2 + methanol CO_2 + ethanol	183–400 bar 45/50 °C	1993 1992	[251] [252]
Taxus cuspidata (yew), needles	Paclitaxel and baccatin III with antineoplastic activity	CO_2 + methanol CO_2 + ethyl acetate CO_2 + dichlomethane CO_2 + ethyl ether	100–300 bar 35–70 °C	1996	[253]
Theobroma cacao (cacao), beans	Pyrazines; influence of pod storage period	CO_2 + methanol CO_2 + dichlormethane	60–200 bar 60 °C	1997	[254]
Triticum aestivum (wheat), germ	Oil enriched in tocopherols	CO_2	250 bar 40 °C	1989	[255]
Uncaria tormentosa, root	Oxindole alkaloids; fractional extraction	CO_2 + methanol	250 bar 60 °C	1997	[256]
Vitis vinifera (white grape), seeds	Phenolic compounds (catechins: gallic acid, catechin, epicatechin), lipids, fatty acids, sterols fractional extraction; solubility data	CO_2 + ethanol CO_2 + methanol	140–450 bar 35–60 °C	1999 1999 2000 2000	[257] [258] [259] [260]

cancer-treatment-tablets [294], benzodiazepines in tablets or capsules [295], tocopherol in tablets or powders [296, 297] and vitamin K_1 in powders [298]. Several authors made a comparison to model matrices for pseudoephedrine from tablets and from a spiked-sand matrix [299], for felodipine from tablets and from a spiked-cotton matrix [300] and for carotene and tocopherol from tablets and a spiked-cellulose matrix [301]. An example for the extraction of polar drugs (sulfamethoxazole and trimethoprim) from a commercial infusion, that represents an aqueous and therefore strongly polar matrix, is given by Mulcahey and Taylor [302].

6. Modelling of the extraction processes

Mathematical models are applied to give a quantitative description of the kinetics of an extraction process. They are generally based on equations describing mass transport phenomena and include specified parameters which can be fitted to extraction data, e.g. yield or content within a specified period of time. In general the extracted material is regarded as one pseudocomponent. A few simplified ideas and approaches on extraction models are discussed below.

According to Brunner [4, 303] the extraction process can be divided into three steps:

- Transportation of substances within the solid material onto the surface (solid phase),
- Transition of substances from the solid into the fluid (interface solid-fluid),
- Transportation of substances with the bulk of extraction gas (fluid phase).

Simplified models do not consider all the three steps but combine some of them to one single step. Assuming a steady state process without any flow of the fluid phase the amount of extract transported per unit of time is proportional to the mass transfer area and to a specified concentration gradient, as required for any mass transport, e.g. laws of Fick or law of Noyes-Whitney. The proportionality constant is given by a mass transfer coefficient for either the mass transport within the solid phase to the interface solid-fluid or the transport from there to the bulk fluid. The reciprocal values of these mass transfer coefficients can be summarized to a reciprocal total mass transfer coefficient. Since mass transfer resistance in the solid is dominant the total mass transfer coefficient is approximately represented by the mass transfer coefficient in the solid phase.

Supercritical extraction processes are usually applied in the dynamic mode and therefore more complex models have to be applied which are also based on the above mentioned steps of mass transfer during the extraction process. They are initially derived from equations describing heat transfer phenomena. One model is the one-dimensional dispersion-single particle model [4, 304]. It is based on a mass balance considering solid and fluid phase. For the latter one plug flow is assumed, represented by a convection-term as well as an one-dimensional axial mass transport by diffusion, usually called axial dispersion. This term is derived from Fick's second law with an axial dispersion coefficient as proportionality constant. The solid phase is considered as a single, spherical and isotropic particle. Then a modified Fick's second law can be used to express the concentration profile within a solid particle. The proportionality factor is determined by the diffusion coefficient of extracted material in the solid material. At the solid-fluid interface both the model for the fluid phase and for the solid phase has to be coupled. If the solvent does not change its phase at the interface (homogeneous extraction) the concentration of extracted substances at the interface must be equal. If the solvent changes its phase (heterogeneous extraction) a partition coefficient has to be taken into account. This is usually given by the thermodynamic equilibrium partition coefficient, which is the quotient of concentration in the fluid and in the solid at the interface solid-fluid. The above-mentioned approaches result in more or less complex equations from which boundary conditions can be derived. Similar to the laws of heat transfer they can be simplified by combining specified parameters to dimensionless groups. They are named Fourier-, Biot-, Bodenstein- and Peclet-number [4]. An approach of solving the differential equations is made by Goodarznia and Eikani [304]. To get an optimized modelling system some more effects occurring during the extraction process have to be considered, e.g. radial distribution of flow velocity, radial and axial concentration profiles in the solid bed, distribution of particle size, etc. [4]. A rough survey of literature dealing with special approaches on modelling should be given below.

Table 5: Other pharmacologically active compounds – preparative scale

Matrix	Targets	Gas	Conditions	Year	Ref.
Achillea millefolium (yarrow), herb	Cholagoga substances; kinetic studies	CO_2	100–400 bar 25–60 °C	1999	[261]
Allium cepa (onion), bulbs	Onion flavours	CO_2	207 bar 37 °C	1995	[262]
Aluminium balls, spiked with carotene	Recovery and degradation of carotene; solubility data	CO_2	300 bar 40–60 °C	2000	[263]
Azadirachta indica (neem), seeds	Neem seed oil (azadirachtin, nimbin, salannin)	CO_2 + methanol	69–344 bar 55 °C	1997	[264]
Bixa orellana (annatto), seeds	Natural food colourants (bixin, norbixin)	CO_2	207–345 bar 50/60 °C	1991	[265]
Capsicum annuum (paprika)	Natural food colourants (carotenes, capsanthin) flavour compounds (capsaicin); frational extraction; enrichment of antioxidative vitamines (carotenoid, tocopherol); kinetic studies and phase equilibria data of CO_2-capsaicin-carotene	CO_2 Propane	90–400 bar 20–60 °C 30–50 bar 25 °C	1998 1999 1999	[266] [267] [268]
Chrysanthemium cinerariae-folium (pyrethrum), flowers	Insecticides (pyrethrin I/II);	CO_2	83–284 bar 40 °C	1995	[269]
Citrus reticulata (mandarin), peels	Enrichment of carotenes; kinetic studies	CO_2 Propane	100–400 bar 35–55 °C 30–50 bar 25 °C	1999	[267]
Citrus sinensis (orange), peels	Enrichment of carotenes; kinetic studies	CO_2 Propane	100–400 bar 35–55 °C 30–50 bar 25 °C	1999	[267]
Cod liver oil/carotene-mixture	Enrichment of carotene; solubility data	CO_2	200–300 bar 40–60 °C	2000	[270]
Elaeis guineensis (palm), palm oil pressing residue and palm tree leaves	Antioxidant vitamins (carotene, tocopherol); free fatty acid content; phase equilibria data of CO_2-tocopherol	CO_2	300–500 bar 70 °C	1995	[271]
Ephedra sinica (ephedra), herb	Cuticular waxes, (nonacosan-10-ol, α-amyrin acetate, squalene, stigmasterol); kinetic studies and scale up	CO_2	100–350 bar 35–50 °C	1996 1997	[272] [273]
Glycine maximus (soy), oil deodorizer distillate, seeds	Tocopherols, fatty acids, sterols, squalene; kinetic studies	CO_2	241–700 bar 40–90 °C	2000 1996	[274] [275]
Hordeum vulgare (barley), fruits	Antioxidant vitamines (tocopherols, tocotrienols); fractional extraction	CO_2 Propane	79–127 bar 40 °C	1998	[276]
Ilex paraguariensis (maté), leaves	Methylxanthines (caffeine, theophylline, theobromine); fractional extraction; kinetic studies	CO_2	138/255 bar 40/70 °C	2000	[277]
Magnolia grandiflora (magnolia), leaves	Sesquiterpene lactones (parthenolide, costunolide); sesquiterpene (cyclocolorenone)	CO_2 Propane	75 bar 40/50 °C 45 bar 40/50 °C	1995	[278]
Mauritia flexuosa (buriti), fruit pulp	Enrichment of carotene; modelling and kinetic studies	CO_2	200/300 bar 40/55 °C	1999	[279]
Medicago sativa (alfalfa), leaf protein concentrate	Natural colourants (carotene, lutein, pheophytin a/b); kinetic studies	CO_2	100–700 bar 40 °C	1988	[280]
Morus alba (mulberry), root bark	Higher molecular compounds (nonacosan-10-ol, α-amyrin acetate, squalene, stigmasterol)	CO_2	100–300 bar 35–60 °C	1997	[273]
Nicotiana tabacum (tobacco), leaf bits, powder, aqueous nicotine solutions	Nicotine; modelling and kinetic studies	CO_2	150–300 bar 50–70 °C	1998	[281]
Oil deodorizer distillate	Enrichment of tocopherols; phase equilibria data	CO_2 + ethanol	130–250 bar 50–90 °C	1991	[282]

Table 5 (continued)

Matrix	Targets	Gas	Conditions	Year	Ref.
Olea europaea (olive), olive oil deodorizer distillate, pomace	Enrichment of squalene; phase equilibria data; antioxidative vitamines (tocopherols); fractional separation	CO_2 CO_2 + ethanol	100–350 bar 40–60 °C	2000 2000	[283] [284]
Oryza sativum (rice), bran	Enrichment of tocopherol; kinetic studies	CO_2	250–700 bar 40/80 °C	1996	[275]
Rosmarinus officinalis (rosemary), leaves	Natural antioxidants (rosmanol, carnosolic acid, carnosol); removal of essential oil	CO_2 CO_2 + ethanol	300–500 bar 40–60 °C	1995 2000	[285] [286]
Salvia officinalis (sage), leaves	Natural antioxidants (carnosolic acid, carnosol); removal of essential oil	CO_2	500 bar 60 °C	1995	[285]
shark liver oil	Enrichment of squalene and diacylglycerylesters; fractional extraction; modelling	CO_2 + ethanol CO_2	250 bar 60 °C	2000 2000	[270] [283]
Silybum marianum (St. Mary's thistle), herb	Cholagoga substances; kinetic studies	CO_2	100–400 bar 25–60 °C	1999	[261]
Solanum lycopersicum (tomato), paste	Natural food colorants (carotene, lycopene); fractional separation	CO_2 + ethanol	200–300 bar 35–65 °C	2000	[287]
Spirodela polyrhiza (greater duckweed), entire plant	Higher molecular compounds (nonacosan-10-ol, α-amyrin acetate, squalene, stigmasterol)	CO_2	100–300 bar 35–60 °C	1997	[273]
Stevia rebaudiana (stevia), leaves	Diterpenic glycosides (rebaudiosides, stevioside); frational extraction; modelling and kinetic studies	CO_2 + ethanol CO_2 + water CO_2 + ethanol + water	120/200 bar 16–45 °C	2000	[288]
Taraxacum officinalis (dandelion), roots	Cholagoga substances; kinetic studies	CO_2	100–400 bar 25–60 °C	1999	[261]
Theobroma cacao (cocoa), beans, butter, nibs	Xanthines (theobromine, caffeine); phase equilibria data of CO_2-(ethanol)-theobromine CO_2-(ethanol)-caffeine CO_2-(ethanol)-cocoa butter	CO_2 + ethanol	80–300 bar 40–95 °C	1992 1996	[289] [290]
Triticum aestivum (wheat), germ	Enrichment of tocopherol; kinetic studies	CO_2	250–700 bar 40/80 °C	1996	[275]
Valeriana officinalis (valerian), root	Cholagoga substances; kinetic studies	CO_2	100–400 bar 25–60 °C	1999	[261]

A more simplified approach to extractions from packed beds is made by neglecting any axial dispersion coefficient and either internal diffusion within the solid material or mass transfer resistance at the interface [305]. Sovova describes a model for the extraction of vegetable oil that combines easily accessible solute of broken cells at the beginning of the extraction with enclosed solute in intact cells [306]; solutions of the differential equations are also proposed. Reverchon and Marrone use a similar approach for the extraction of various oil seeds [307]. It takes into account axial dispersion and distinguishes between free and tied solute. The proportion of broken cells in the solid phase is considered as well. Starting from experimental results on the extraction of alkaloids from *Crotalaria spectabilis* by ethanol-modified carbon dioxide [210] a mathematical model is derived [308]. It combines thermodynamic models of ethanol-carbon dioxide mixtures with simplified mass transfer models of the solute, without considering a single particle. The same mass transfer model is applied for the extraction of vegetable oils [309, 310]. Isotropic monosized spheres as well as concentration of extracted material in the fluid approximately to zero is assumed by Bartle et al. [311, 312]. The concentration profile within a solid particle is integrated over the whole particle volume. They also consider solubility effects in this dynamic extraction model [312]. A single-particle model according to Fick's second law for the extraction of essential oils is extended to a whole bed extraction model [313]. It is assumed that each particle has the same volume and consequently the mass transfer of a packed bed can be summarized from all single particles. Some models dealing with more than one component (multicomponent models) during the extraction process are described in [314] with a special regard on the shrinking-core model. It is applied to the extraction of vegetable as well as essential oils and takes into consideration that the diffusion length within a single particle increases during the extraction process. Goto et al. [315] give a similar approach for multicomponent mixtures. Some authors have applied completely different approaches for modelling the extraction process like a desorption model from the surface of an inert matrix described by Pawliszyn [316].

7. Phase equilibria data

7.1. Determination of phase equilibria data

Phase equilibria data are an important tool for design and viability of supercritical fluid extraction with or without application of modifiers. A theoretical and practical survey of phase equilibria measurement is given by Brunner [4].

There are three methods available to determine high-pressure phase equilibria data, which are briefly discussed below.

7.1.1. Static-analytical method

Solid or liquid solutes are placed in a thermostated high-pressure equilibrium cell. The supercritical solvent (pure or modified gas) is pumped into the equilibrium cell until the desired pressure is reached. In most cases the adjustment of equilibrium state is accelerated by stirring or recirculating of either supercritical phase or both liquid and supercritical phase. Dissolving of solute in the supercritical solvent causes a pressure drop, therefore equilibrium state can be assumed if no pressure decrease can be determined anymore (usually varies between one and some hours). When equilibrium is reached agitation is stopped and the phases separate due to their difference in density. Samples are taken from each phase by expanding a small amount of each phase through a thin capillary into a flask. The amount of solvent (gas) is measured volumetrically; the mass of solute can be determined either gravimetrically in case of one component or by a special analytical method (HPLC, GC) in case of multicomponent solutes. The equilibrium cells have a relatively high volume (about 1000 cm^3) and thus high amounts of solute and solvent are required as well. Since samples of the equilibrium phases are analysed separately, phase equilibria measurement of multicomponent systems favours the static-analytical method. Errors occur especially at sample drawing, e.g. pressure drop and residues in sample lines [4].

7.1.2. Synthetic method

A synthetic type apparatus consists of a thermostated high-pressure equilibrium cell with at least two windows for viewing into the interior part of the cell. The volume of the cell can be varied, usually by means of a movable piston inside the equilibrium cell. The content of the cell is stirred magnetically. Since the composition of the phases are not analysed, well-known amounts (determined by weighing the cell) of solid or liquid solute as well as supercritical solvent are brought into the equilibrium cell. When the desired temperature is reached, the pressure inside the equilibrium cell is changed by removing the piston while keeping the temperature constant. Usually the pressure is increased until only one single phase can be observed. Then the pressure is continuously decreased. Depending on the starting composition of the system additional phases will appear at certain pressures. The syn-

Table 6: Phase equilibira data of vegetable oil compounds

Substances	Conditions	Gas/method	Year	Ref.
Behenic acid	80–160 bar 35–45 °C	CO_2 + methanol static-analytical	1999	[318]
Caprylic acid (ester with glycerol)	50–322 bar 40–120 °C	CO_2 static-analytical/synthetic	1997	[319]
Fatty acids	20–120 bar 40–80 °C	CO_2 Ethane static-analytical	1991	[320]
Fatty acids; fatty acid methyl esters	38–288 bar 40/60 °C	CO_2 static-analytical	1990	[321]
Fish oil ethyl esters	90–250 bar 40–80 °C	CO_2 static-analytical	1999	[322]
Glycerides	50–210 bar 25–75 °C	CO_2 synthetic	1993	[323]
Laurylic acid (esters with glycerol)	150–400 bar 35–60 °C	CO_2 dynamic	1993	[324]
Milk fat	100–310 bar 40/60 °C	CO_2 static-analytical	1992	[325]
Oleic acid	96–200 bar 35/45 °C	CO_2 dynamic	1991	[326]
Oleic acid/methyl oleate-mixture	45–262 bar 40/60 °C	CO_2 static-analytical	1993	[327]
Olive oil	138–302 bar 40–80 °C	CO_2 static-analytical	1996	[328]
Palm oil	50–106 bar 50–80 °C	CO_2 synthetic	1987	[329]
Squalene; free fatty acids and -esters	230 bar 57–97 °C	CO_2 static-analytical	1999	[330]
Stearic acid	90–165 bar 45 °C	CO_2 + acetic acid CO_2 + methyl acetate static-analytical	1997	[331]
Triglycerides	150–350 bar 40 °C	CO_2 dynamic	1992	[332]
Triglycerides; fatty acids	80–300 bar 40 °C	CO_2 dynamic	1998	[333]

Table 7: Phase equilibria data of essential oil compounds

Substances	Conditions	Gas/Method	Year	Ref.
Camphor; fenchone; limonene; pinene	60–126 bar 40–60 °C	CO_2 static-analytical	1999	[334]
Citral; limonene	70–100 bar 37–50 °C	CO_2 synthetic	1995	[335]
Citral; limonene	30–110 bar 35–50 °C	CO_2 dynamic	1989	[336]
Lemon oil; limonene/ citral-mixture	50–106 bar 50–80 °C	CO_2 synthetic	1987	[329]
Limonene; linalool	69–111 bar 45/55 °C	CO_2 dynamic	2000	[337]
Orange oil	71–137 bar 50–70 °C	CO_2 synthetic	2000	[338]

thetic method uses small equilibrium cells and thus small sample amounts. It is suitable for measuring phase equilibria of binary systems or the determination of boundary lines in multicomponent systems. Sources of error are the determination of total composition at the beginning and the measurement of the equilibrium pressure [4].

7.1.3. Dynamic method

The solute, usually mixed up with an inert matrix, is placed in a thermostated equilibrium cell. Unloaded pure or modified solvent is set to the desired temperature and pressure and passes continuously through the equilibrium cell. During the short residence time of the supercritical solvent in the cell, equilibrium concentration is assumed to be adjusted. Saturated gas leaves the equilibrium cell and is depressurised to atmospheric pressure. Measuring of gas volume and analysing of solute can be done analogically to the static analytical method. Because of accumulation of the solute, the dynamic method can be used even if solubility in the supercritical phase is very low. The greatest problem is to establish equilibrium during the short residence time of the supercritical solvent. The method is used particularly for one-component solutes. For multicomponent solutes changes in the solute due to different equilibrium solubilities as well as in the supercritical solvent have to be taken into account [4].

7.2. Phase equilibria data in the literature

For a lot of substances and multicomponent mixtures that are relevant in SFE, phase equilibria data are published over a wide pressure range. For more polar substances phase equilibria data including modifiers are also available. Depending on the system and target of the measurement either the static-analytical, synthetic or dynamic method has been applied. Literature dealing with phase equilibria data of vegetable oil, essential oil and other pharmacologically active compounds are compiled in Table 6, Table 7 and Table 8, respectively.

8. Other applications of supercritical fluids

8.1. Supercritical fluid chromatography

Supercritical fluid chromatography (SFC) is a separation method, which has been derived from HPLC. It can be utilized in analytical and in preparative scale as well. The mobile phase consists of a supercritical or a near-critical fluid. Pure gases can be used, but mostly they are combined with more or less polar modifiers. Stationary phases are mainly adopted from well-established sorbents used in HPLC. Detailed reviews about both, carbon dioxide based mobile phase, including also phase equilibria data [19], and stationary phases [359] are available. Brunner gives a detailed overview of SFC as separation method [4]. Starting from general aspects of SFC he describes technical requirements and theoretical approaches for scale-up. An actual review about applications of SFC has been published by Chester and Pinkston [360].

8.2. Particle design

In the last few years particle design by means of supercritical fluids has gained more and more importance. Depending on the method and conditions micron or submicron particles can be obtained, as well as particles with alternative morphological or solid state forms. The supercritical fluid, which is required either as solvent or as antisolvent, consists of a pure or modified gas, which is mostly carbon dioxide. General reviews on particle formation by supercritical fluids are available [361–363]. Particle formation processes can be divided into three main groups [362], which should be briefly described.

8.2.1. Precipitation from supercritical solutions

Solid material is dissolved in a supercritical fluid under high pressure. This solution is rapidly expanded, thus the density decreases suddenly. With declining density the solvent capacity is reduced by orders of magnitude so that micron or submicron particles are formed by homogenous nucleation. If the solution is rapidly expanded to atmospheric pressure, the supercritical solvent suddenly evaporates and strong aerosolation effects occur in addition. This procedure is called rapid expansion from supercritical solution (RESS). The yields are rather small, due to the very low solubility of organic or biological material in supercritical fluids, particularly carbon dioxide. Special surveys of the RESS process are available [364, 365]. Alessi et al. give a review about particle production of steroid drugs by the RESS process [366].

8.2.2. Precipitation with supercritical fluids as antisolvent

The low solubility of organics in supercritical solution is overcome by dissolving the organic material in conventional liquid solvents. Starting from these solutions particles can be formed in two different ways. The first one is called gas antisolvent (GAS); solution and supercritical fluid are brought together in a vessel and mixed up. Due to a relatively high solubility of supercritical fluids in organic solvents, the volume of the solution is expanded, thus the density decreases. The solvent capacity is reduced by orders of magnitude and fine solid particles precipitate out of the solution because of the antisolvent effect. For the second way at least three terms are common. Precipitation from compressed antisolvents (PCA) is the general expression but supercritical antisolvent (SAS) process and aerosol spray extraction system (ASES) are also used. The solution is sprayed by a fine nozzle into the supercritical fluid as antisolvent and fine particles are formed by precipitation. A special application of this type is the solution enhanced dispersion by supercritical fluids (SEDS). The

Table 8: Phase equilibria data of pharmacologically active compounds

Substances	Conditions	Gas/Method	Jahr	Ref.
Antibiotics (polycyclic ethers)	140–400 bar 60–80 °C	CO_2 + methanol CO_2 + water static-analytical	1992	[339]
Antioxidants (ascorbic acid, gallic acid, butylhydroxyanisole, tocopherol)	130–250 bar 35–60 °C	CO_2 dynamic	1999	[340]
Caffeine (partition coefficient)	80–300 bar 40–60 °C	CO_2 + water static-analytical	1996	[341]
Capsaicin	70–400 bar 25–60 °C	CO_2 static-analytical	1992	[342]
Carbonic acids	23–240 bar 35–120 °C	CO_2 synthetic	2000	[343]
Chlorophyll	120–200 bar 35 °C	CO_2 Ethane synthetic	1990	[344]
Colourants (carotene, lutein, capsanthin, bixin, curcumin, pheophytin)	50–800 bar 15–55 °C	CO_2 + ethanol synthetic	1991	[345]
Coumarins	74–405 bar 40–100 °C	CO_2 dynamic	1990	[346]
Coumarins	85–250 bar 35–50 °C	CO_2 dynamic	1998	[347]
Estradiol; fluorouracil	100–220 bar 35–55 °C	CO_2 + ethanol dynamic	2000	[348]
Gingerol	127–196 bar 50/65 °C	CO_2 static-analytical	1990	[349]
Lutein diesters	115–316 bar 40 °C	CO_2 + several modifiers dynamic	2000	[350]
Monosaccharides (glucose, fructose)	40–214 bar 35–75 °C	CO_2 static-analytical	1994	[351]
Penicilline	100–350 bar 40–60 °C	CO_2 dynamic	1999	[352]
Phenoxymethylpenicilline	80–280 bar 32–52 °C	CO_2 dynamic	1991	[353]
Phenylacetic acid	84–195 bar 35/45 °C	CO_2 dynamic	1990	[354]
Resveratrol	80–140 bar 40 °C	CO_2 + ethanol dynamic	2001	[355]
Salicylic acid	87–157 bar 35/45 °C	CO_2 + ethanol static-analytical	1996	[356]
Steroids (progesterone, testosterone, cholesterol)	80–250 bar 35–60 °C	CO_2 + N_2O dynamic	1992	[357]
Vanillan	84–195 bar 35/45 °C	CO_2 dynamic	1990	[354]
Vanillin (partition coefficient)	80–300 bar 40–60 °C	CO_2 + water static-analytical	1996	[341]
Wool wax	250–650 bar 31–150 °C	CO_2 static-analytical	1997	[358]

organic solution and the supercritical antisolvent are brought together in the mixing chamber of the nozzle, before being finely dispersed in a precipitation vessel [362]. A detailed review about the SAS process is given by Reverchon [367].

8.2.3. Precipitation from gas saturated solutions

Compared to the above-mentioned methods, precipitations from gas-saturated solutions (PGSS) are scarcely applied. A supercritical fluid is dissolved in the molten solute to a high-pressure supercritical fluid saturated solution. This solution is expanded by a nozzle to atmospheric conditions where the volatile gas evaporates and fine particles are formed [362].

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Received July 27, 2001
Accepted August 14, 2001

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