Chapter 3
Supercritical Fluid Extraction: A Global Perspective of the Fundamental Concepts of this Eco-Friendly Extraction Technique

Susana P. Jesus and M. Angela A. Meireles

Abstract Supercritical fluid extraction (SFE) is a green technology that has been applied on a commercial scale for more than three decades. SFE is a high-pressure extraction method in which a mixture of solutes is separated from a solid matrix by bringing the mixture into contact with a fluid in the supercritical state. A supercritical fluid has very particular and unique characteristics, which enable its use as an efficient extraction solvent. Carbon dioxide (CO_2) is the most commonly used supercritical fluid and has applications in food, cosmetic, pharmaceutical, and correlated industries. Many research works have already demonstrated that SFE is a technically feasible process that may also be commercially competitive in terms of economic viability. Although SFE is commercially carried out in several countries, it is nonetheless still considered as an emerging technology. This emerging status remains associated with SFE technology because the conventional low-pressure extraction methods remain the most frequently used extraction techniques, in particular due to the comparatively low cost of investment that is required for installing a low-pressure industrial plant. The physical phenomena that occur during SFE have already been extensively investigated, and there is consensus that SFE is a complex phenomenon that involves multicomponent systems. However, various simplifications can be performed to describe SFE for the purpose of process design. Presently, one of the major challenges for researchers in this area is the proposition of practical procedures (experimental and/or calculation methods) in order to simplify the determination of some process parameters which are required for the studies of economic feasibility. This chapter presents the fundamental concepts of SFE and gives special attention to the information that must be available to conduct preliminary studies of process design and cost estimation.

S.P. Jesus • M.A.A. Meireles (✉)
LASEFI/DEA/FEA (School of Food Engineering)/UNICAMP (University of Campinas),
Rua Monteiro Lobato, 80, Campinas-SP, CEP:13083-862, Brazil
e-mail: meireles@fea.unicamp.br

F. Chemat and M. Abert Vian (eds.), *Alternative Solvents for Natural Products Extraction*, Green Chemistry and Sustainable Technology,
DOI 10.1007/978-3-662-43628-8_3,

3.1 The Supercritical Fluid Extraction Technique

The consumers’ increasing concern about environmental issues and human health has motivated the development of green technologies and the search for natural ingredients with bioactive properties. In fact, the natural products market has presented a progressive and continuous growth in the last decades. Natural matrices are complex multicomponent systems, and so the selective separation of specific substances is a difficult task that requires efficient extraction methods [1]. Rostagno and Prado [1] recently published a book that presents a global view of the state-of-the-art techniques for the extraction and processing of natural products. These authors claim that there is a need for more efficient and selective processes, which can improve the overall quality of natural products and also enable the development of innovative products [1]. Nonetheless, most of the industries still use conventional techniques that are based on outdated technologies. Considering this scenario, the supercritical fluid extraction (SFE) is a particularly interesting alternative to extract bioactive compounds from natural sources. Therefore, the SFE process has many potential applications in food, pharmaceutical, and cosmetic industries.

The SFE is a high-pressure extraction method that has been carried out on a commercial scale since the 1980s. The industrial-scale applications of SFE comprise the decaffeination of green coffee beans and black tea leaves; the production of hop extracts; the extraction of essential oils, oleoresins, and flavoring compounds from herbs and spices; the extraction of high-valued bioactive compounds from different natural matrices; the extraction and fractionation of edible oils; and the removal of pesticides from plant material [2, 3]. At the very early stages of this technology, very large vessels (up to 40 m^3) were sometimes built. Later, the extractors’ capacity became smaller, and today, most extractor vessels have a volume that is equal to or smaller than 1 m^3 [3].

According to Brunner [3], the costs of SFE processes are competitive. Furthermore, in particular cases, SFE processing is the only way to satisfy the product specifications. A significant number of SFE industrial plants of various capacities have been built since the 1980s. Most of the plants are distributed within Europe, the USA, Japan, and the Southeast Asian countries. The state-of-the-art technology that is necessary to design a SFE plant is commercially available. Standard designs can be acquired from many suppliers, and special designs can be custom tailored for a particular process [3].

SFE is a unit operation that performs the separation of a mixture of solutes from a solid matrix by bringing the mixture in contact with a supercritical solvent [4]. The solid material is placed in an extraction cell, forming a fixed bed of solid particles. The supercritical fluid flows continuously through the fixed bed and dissolves the extractable components of the solid [2]. The mixture of solutes that is removed from the solid matrix is named the extract. SFE processes are usually carried out in batch and single-stage modes because solids are difficult

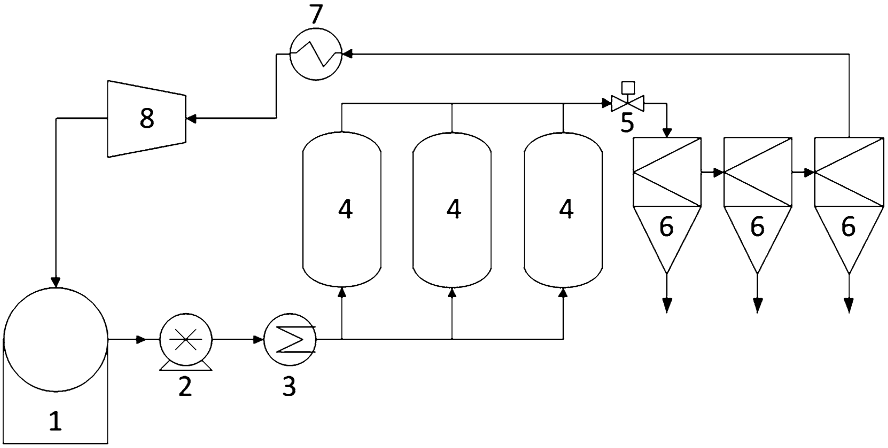


Fig. 3.1 A simplified flowchart of the SFE process (*1* CO_2 storage tank, *2* solvent pump, *3* heat exchanger, *4* extractor, *5* pre-expansion valve, *6* separator, *7* cooler, *8* compressor; the system contains several temperature and pressure controllers that are not shown) (Adapted from Pereira and Meireles [7], with kind permission from Springer Science and Business Media)

to handle continuously in pressurized vessels and separation factors are high [3]. Nonetheless, the modification of the process from batch to continuous mode can be performed by arranging two or more extractors in the process line [5, 6]. This change allows the system to operate continuously despite the occurrence of solid matrix exhaustion. Then, the arrangement of *n* extractors (where $n \geq 2$) operating in a parallel configuration results in the continuous production of the extract by intercalating the charge/discharge times of the *n* extractors in the plant. Plant operation in a continuous mode occurs according to the following format: while one extractor is in the charge/discharge step, the other $n-1$ extractors are in the extraction step [6]. This operating mode presents the advantages of reducing the process setup time and increasing productivity, which leads to a reduction of the operating costs [3, 6].

A simple SFE process comprises two major steps: extraction and separation. In the extraction step, the solvent is fed into the system and is uniformly distributed throughout the extractor. The solvent flows through the solid matrix, extracting the soluble compounds. In the separation step, the loaded solvent (the mixture formed by solvent + extract) is removed from the extraction cell and fed into the separator (flash tank), where the mixture is separated by a rapid reduction of the pressure. The extract precipitates in the separator, while the solvent is removed from the system and is delivered to a recycling step. The solvent is cooled and recompressed and then returns to a storage tank, which feeds the extraction system [2, 7]. A schematic diagram of the SFE process is shown in Fig. 3.1.

3.2 The Supercritical Fluid

A pure component is considered to be in the supercritical state when both its pressure (P) and temperature (T) are higher than their critical values (P_C and T_C, respectively) [2]. The supercritical region is illustrated in the phase diagrams presented in Figs. 3.2 and 3.3. In this region, the fluid can be considered either an expanded liquid or a compressed gas [4].

Supercritical fluids (SCFs) show very particular and unique characteristics that enable their use as efficient solvents. The densities of SCFs are relatively high (compared to gases), and consequently, SCFs have high solvation power. Furthermore, the density can be easily tuned by varying the system pressure or temperature. This particular effect provides these fluids with a certain degree of selectivity, which is useful for the extraction process and allows for easy solvent-solute separation. The separation step can be performed by either decreasing the pressure or increasing the temperature of the mixture (solvent + extract) leaving the extraction column [4]. In the supercritical state, liquid-like densities are approached, while the viscosity is near that of normal gases, and the diffusivity is approximately two orders of magnitude higher than that of the liquid forms [3]. Therefore, in comparison to a gas, a supercritical fluid (SCF) has higher density; in contrast, compared to a liquid, the SCF possesses lower viscosity and a higher diffusion coefficient. All of these characteristics result in a greater solvation power, which allows high extraction rates when SCFs are applied as solvents.

Supercritical carbon dioxide (SC-CO_2) is the most commonly used solvent for applications of SFE in the food, cosmetic, pharmaceutical, and other similar industries. According to Rosa and Meireles [4], two important justifications for the choice of CO_2 are its low critical temperature ($T_C = 304.2$ K) and mild critical pressure ($P_C = 7.38$ MPa). Additionally, CO_2 is not only cheap and readily available at high purity but is also safe to handle (nontoxic and nonflammable) and easily removed by simple expansion to common environmental pressure values [3]. Some

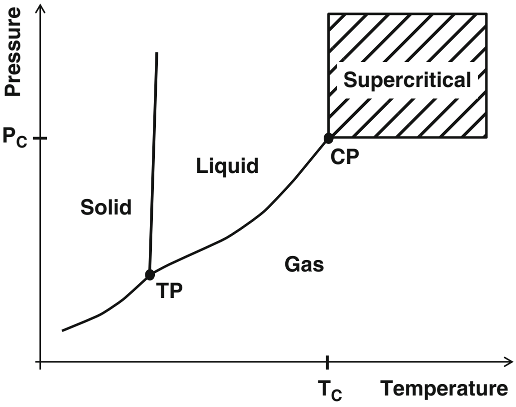


Fig. 3.2 A pure component P × T (pressure vs. temperature) diagram: the supercritical region is indicated by the hatched lines (*TP* triple point, *CP* critical point, P_C critical pressure, T_C critical temperature) (Adapted from Brunner [2], with kind permission from Springer Science and Business Media)

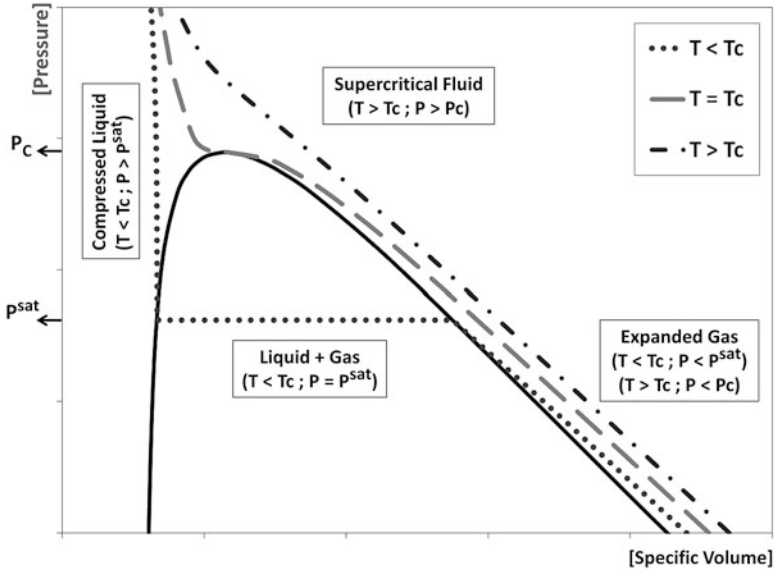


Fig. 3.3 Schematic illustration of a pure component P × V (pressure vs. volume) diagram (T temperature, T_C critical temperature, P pressure, P_C critical pressure, P^{sat} saturation pressure)

well-noted advantages of the SFE process are the solvent recycling possibility, low energy consumption, adjustable solvent selectivity, prevention of oxidation reactions, and production of high-quality extracts.

The properties of SC-CO_2 can be modified over relatively wide ranges. The solvent power of SC-CO_2 is high for hydrophobic or slightly hydrophilic components and decreases with increasing molecular weight [3]. Generally, when the operational pressure is increased, more hydrophilic compounds can also be extracted. If the goal is the extraction of more hydrophilic compounds, then the solvent polarity can be increased by the addition of a polar solvent. The added solvents are named the cosolvents or modifiers [4]. The cosolvent is generally a solvent of high polarity, such as water or ethanol. These two solvents are conveniently selected because both are classified as GRAS (generally recognized as safe). Therefore, the green concept of supercritical technology is perfectly maintained. The cosolvent takes the form of a compressed liquid (see Fig. 3.3) when held in the usual operational conditions of the SFE process.

3.3 The Solid Matrix

In natural sources, the soluble portion of the solid matrix is generally composed of several different classes of organic compounds. As a result, the extract (or solute) is a complex mixture of chemical species, such as terpenes, terpenoids, flavonoids, alkaloids, and many other compounds [8]. The soluble fraction may be located inside cellular structures and may interact very strongly with the nonsoluble components of the raw material. Therefore, vegetable raw materials often pass through a pretreatment process to facilitate solvent access to the solute and to increase the solute-solvent interactions.

3.3.1 Raw Material Pretreatment

In SFE, the raw material commonly passes through a pretreatment stage before it is fed into the fixed bed extractor. Pretreatment is performed to prepare the solid particles, allowing the best possible efficiency to be achieved in the extraction process. In most cases, the pretreatment process comprises one or more of the following steps:

- *Drying*: A drying step is often used to adjust the water content of the solid matrix. If the target compound is a nonpolar or slightly polar substance, then the water content is reduced to increase the extraction efficiency. However, if the target compound has a more polar structure, the drying process may not be necessary or adequate. In some cases, the initial water contained in the solid particles can act as a cosolvent and improve the extraction efficiency of certain polar compounds.
- *Milling*: The main purpose of the milling step is the reduction of the solid particle sizes to enlarge the interfacial solid-fluid mass transfer area. Furthermore, the milling process may also cause the destruction of some plant cellular structures and, consequently, facilitate solvent access to the solute. Nonetheless, reducing the particle size also increases the degree of compaction of the solid substrate. Excessive bed compaction must be avoided because it can result in the formation of preferential pathways of solvent access, preventing the solvent from reaching all of the extractable material [5].
- *Sieving*: A sieving step is generally applied to standardize the size of the solid particles. Some particles may be discarded according to the particle diameter range of interest.
- *Chemical reaction*: A reaction step is not commonly applied, but it can be useful in particular cases. A chemical reaction may be performed to free the target solutes and improve the extraction efficiency.

3.4 The Definition of the Pseudoternary System

In SFE from natural matrices, the obtained extracts are complex mixtures composed of different groups of chemical compounds. Therefore, the extract is always a multicomponent system. Additionally, the solid matrix is a very complex mixture that can contain intact cellular structures, as well as broken cellular structures [8, 9].

Knowledge of the system's composition and the physical phenomena that occur inside the extraction bed is essential for creating a detailed description of the SFE process. This knowledge is also fundamental to decision making with respect to simplifying the description of the phenomena that take place within the extraction cell. With respect to composition, some assumptions may be used to facilitate the description of the SFE system (solid material + solvent). According to Rodrigues et al. [8], a very simplified picture of the system is developed when it is treated as been formed by three pseudocomponents (extract + cellulosic structure + solvent), which are defined below:

- *Extract (or solute)*: The extract is a multicomponent mixture composed of the solids that are soluble in the extraction solvent. The extract interacts with both the supercritical solvent and the cellulosic structure [8].
- *Cellulosic structure (or inert material)*: The cellulosic structure is formed by a multicomponent mixture that contains all of the solids that are insoluble in the supercritical solvent. It is crucial to note that although being inert to the solvent action, the cellulosic structure interacts strongly with the extract [8].
- *Solvent*: The solvent can be either a pure component (the fluid in the supercritical state) or a mixture of the supercritical fluid and a cosolvent. In the typical operating conditions of SC-CO_2 extraction, the cosolvent (water, ethanol, among others) is a compressed liquid.

3.5 Thermodynamic Aspects

The design of an engineering project of a SFE system requires knowledge of the limitations that control the extraction process. According to Ferreira and Meireles [10], the constraints of the SFE are related to two aspects: (a) the thermodynamics (solubility and selectivity) and (b) the mass transfer phenomena. A discussion of the first is presented in this section, while the second aspect is treated in Sect. 3.6.

3.5.1 Equilibrium Solubility (Y)*

The driving potential for mass transfer is determined by the difference relative to the equilibrium state. According to Brunner [3], the phase equilibrium provides information regarding (a) the capacity of the supercritical solvent, which is directly related to the solubility of a specific solute in the solvent (the solubility is the amount of a solute that is dissolved by the supercritical solvent at thermodynamic equilibrium); (b) the selectivity of a supercritical solvent, which can be described as the ability of a solvent to selectively dissolve one or more compounds; and (c) the dependence of these two solvent properties on the conditions of state (P and T). If the capacity and selectivity are known, a guess can be made regarding whether a separation problem can be solved using a supercritical solvent [3].

It should be noted that two different approaches can be adopted when considering the equilibrium solubility of an extract within a supercritical fluid, including (a) the solubility of the pseudobinary system (Y_{BIN}*), which is composed only of the extract + solvent, and (b) the solubility of the pseudoternary system (Y_{TER}*), as described in Sect. 3.4 (cellulosic structure + extract + solvent). It is well known that the cellulosic structure strongly interacts with the extract. Thus, the solubility of a solute as measured in the pseudobinary system differs significantly from the solubility of the same solute when measured in the pseudoternary system [9]. A good example of the influence of the cellulosic structure on the solubility value is given by Brunner [2]: the solubility of pure caffeine in SC-CO_2 (binary system) is approximately 20 times greater than the solubility of caffeine measured for the pseudoternary system (caffeine + coffee grains + SC-CO_2) at the same conditions of temperature and pressure. Brunner [2] also mentioned that the concentration of caffeine in the supercritical solvent throughout most time of the SFE process is less than 100 ppm. This value is significantly below the solubility of caffeine as measured for the pseudoternary system ($Y_{TER}* = 200$ ppm at $T = 350$ K and $P = 30$ MPa). Then, it can be said that when the solubility of the pseudoternary system is relatively high (as in the caffeine example), the mass ratio of the solute in the fluid phase (Y) will likely be significantly lower than Y_{TER}* during typical SFE operational conditions.

Equilibrium solubility is only reached under specific processing conditions. A detailed discussion of the experimental determination of the pseudoternary solubility is presented by Rodrigues et al. [8]. These authors used the dynamic method to measure the pseudoternary solubility of extracts from three vegetable raw materials (clove buds, ginger, and eucalyptus). In the dynamic method, a typical SFE experiment is performed: the solvent is continuously fed into an extraction column at a given pressure and temperature using a solvent flow rate (Q_{CO2}) that assures saturation at the exit of the column [4]. Rodrigues et al. [8] demonstrated that there is a particular solvent flow rate (denoted Q*) at which the equilibrium is achieved and the solubility must be measured. Therefore, the use of the dynamic method requires that a certain set of experiments must be performed to determine the specific solvent flow rate at which the solvent leaves the extraction cell under the saturation condition [11]. This is necessary because, under large flow rates, there is insufficient contact time to guarantee that the solvent is saturated. However, at very low solvent flow rates, axial dispersion may interfere with the measurement of solubility. Hence, there is an optimum solvent flow rate that is a function of the raw material and the thermodynamic state (P and T) used in the SFE process [4, 11].

In the dynamic method, the equilibrium solubility is given by the slope of the linear part of the overall extraction curve (OEC) (this curve is discussed extensively in Sect. 3.6.2). The work presented by Rodrigues et al. [8] showed that the experimental determination of Y_{TER}* requires a slow, tedious, and costly experimental investigation because it is necessary to determine the CO_2 flow rate that can be used safely for the measurement of the equilibrium solubility [9]. In some works, the solubility is simply calculated by using the slope of the linear part of an OEC determined under a random solvent flow rate (i.e., $Q_{CO2} \neq Q$*). Meireles

[9] states that in this case, the measured value should be referred to as $Y_{S/F}$* and that there is a clear difference between Y_{TER}* and $Y_{S/F}$*. This author also mentioned that the difference can be understood by recalling that to measure the first value (the true solubility in the pseudoternary system), it is expected that equilibrium is achieved during the extraction experiment (i.e., Q_{CO2} must be equal to Q*). In the second case, the "solubility" ($Y_{S/F}$*) is measured at a given solvent-to-feed (S/F) mass ratio using a random solvent flow rate. In the latter case, there is no guarantee that the saturation of the solvent is reached; thus, the value of $Y_{S/F}$* cannot be treated as the real equilibrium solubility.

3.5.2 Global Yield Isotherms (GYI)

When studying a SFE system, one of the first fundamental steps is the selection of the temperature and pressure parameters, which must be chosen by taking into account the quality and purity of the obtained extract. The quality of an extract is determined by its chemical composition, which is directly related to the selectivity of the solvent. Thus, a set of experiments must be performed based on various combinations of temperature and pressure because both thermodynamic parameters are strongly related to selectivity and solubility. These experiments deliver information regarding the solvent density, which is directly associated with the solvent power and consequently with the adjustable selectivity of SC-CO_2. Moreover, these experiments also provide information regarding the solubility of the solute in the supercritical solvent. According to Carvalho et al. [12], the investigation of a SFE process requires some knowledge of the behavior of the system of "solid material + CO_2." The interactions of the extract with both the solvent and cellulosic structure are fundamental to understanding the extraction process. However, very little is known regarding these interactions because they involve multicomponent systems of high complexity. The extension of these "solute-solvent" and "solute-cellulosic structure" interactions can be evaluated through two types of experiments: (a) the determination of the solubility of the pseudoternary system (as previously discussed in Sect. 3.5.1) under different conditions of temperature and pressure and (b) the results of the global yield isotherms (GYI) [12]. In GYI experiments, an exhaustive extraction is conducted under different conditions of temperature and pressure.

Meireles [9] claimed that to obtain reliable results for Y_{TER}*, the experiments used to determine solubility must be performed in a SFE unit containing an extractor vessel with a volume of at least 50 cm^3. This requirement is because in these experiments, an overall extraction curve (OEC) (see Sect. 3.6.2) must be built; thus, the use of small amounts of feed material is generally associated with relatively high experimental errors. Moreover, the solubility measurements require difficult experimental work (as discussed in Sect. 3.5.1). However, the GYI experiments are comparatively easy to conduct because they only require an exhaustive extraction.

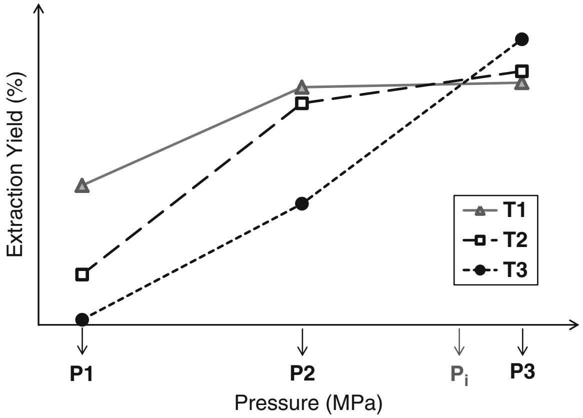


Fig. 3.4 Schematic illustration of the global yield isotherms (T1 < T2 < T3, P1 < P2 < P3, *Pi* crossover pressure) (the experimental points were connected by lines only to evidence the crossover point) (Adapted from Jesus et al. [13])

In this case, extractor vessels of small volumes (such as 5 cm^3) and, consequently, small amounts of the feed material can be safely used to perform GYI assays because there is no need to build an OEC [9]. Therefore, taking into account all the aspects cited above, it is apparent that the choices of operating temperature and pressure may be easier upon consideration of the results of GYI experiments.

In terms of the total extraction yield or the yield of a specific target compound, the results from GYI assays are generally plotted on a graph similar to the schematic illustration presented in Fig. 3.4. From this plot, it is possible to evaluate the effects of the parameters temperature and pressure on the extraction yield. Taking into account an isothermal condition, the effect of operational pressure can be understood. It is clear that a rising pressure results in an increasing extraction yield. This effect is attributed to the increase in CO_2 density and, consequently, the enhancement of its solvation power (although, a higher solvation power may be associated with lower selectivity) [13]. The effect of the operational temperature in SFE is typically more complex due to the combination of two variables, density and vapor pressure. The vapor pressure of the solute increases with temperature, causing increased solubility. However, the solvent density decreases with increasing temperature, causing reduced solubility [11]. As a result, these two variables cause inverse effects on the extraction yield. It is well known that the dominant effect depends on the magnitudes of both effects individually.

At relatively low pressures ($P < Pi$, according to Fig. 3.4), the effect of solvent density prevails; thus, increasing the temperature results in a reduction of the extraction yield. However, at relatively high pressures ($P > Pi$, according to Fig. 3.4), the effect of vapor pressure dominates; as a result, increasing the temperature enhances the extraction yield [2, 11, 13]. The pressure at which the inversion of the dominant mechanism occurs is known as either the crossover point or the crossover pressure. From the GYI graph (Fig. 3.4), it can be said that the crossover pressure (*Pi*) falls somewhere between P2 and P3. At pressures less than *Pi*, the solvent density always dominates, while at pressures higher than *Pi*, the dominant mechanism is the solute vapor pressure. The crossover point is a characteristic of each SFE system (solvent + solute + cellulosic structure) and must be experimentally determined for each distinct pseudoternary system.

Generally, when working with SFE from natural matrices, the major goal is to produce extracts that are enriched in bioactive compounds. As a result, it is important to hold in mind that the selection of the operating temperature and pressure must be made by taking into account the extract characterization in terms of its chemical composition and functional properties. To do so, the extracts obtained in the GYI experiments should be characterized using appropriate methods, such as gas chromatography with flame ionization detection (GC-FID), gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and ultraviolet spectrophotometry, among others [9]. Additionally, the bioactive properties of the material should also be investigated, particularly if the production of nutraceutical products is the purpose of the extraction process.

3.6 Mass Transfer Aspects

The mass transfer mechanisms that occur in SFE from natural solid matrices are not readily understood. The difficulties encountered in describing and modeling the SFE process arise from the fact that SFE involves multicomponent systems with a significant number of components, which can belong to many different chemical classes. Therefore, it is very difficult to establish the interactions between the solvent, the solutes, and the solid matrix [10].

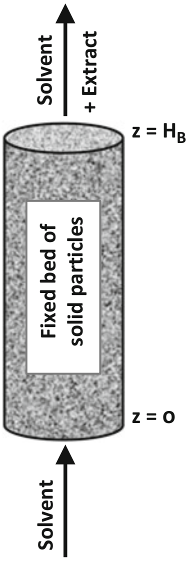
3.6.1 The Mass Balance Equations in the Fixed Bed Extractor

The SFE process is generally performed in a fixed bed extractor of cylindrical shape. The solid particles are packed in the extraction cell, forming a fixed bed through which the supercritical solvent is continuously flowed. A schematic representation of the fixed bed extractor is shown in Fig. 3.5.

It is crucial to propose simplifications when carrying out calculations of the process design. Some simplifications must be assumed to reduce the problem to one that is mathematically tractable. To simplify the description of the SFE process, the extraction system is usually treated as a pseudoternary (cellulosic structure + extract + solvent) and biphasic system (fluid phase + solid phase). The fluid phase (solvent + extract) and the solid phase (cellulosic structure + extract) are both pseudobinary systems [9, 14]. A schematic diagram of the components inside the fixed bed extractor is presented in Fig. 3.6.

When evaluating the mass balance of SFE, it is typical to assume that the extraction cell is a cylindrical bed in which the solid particles are homogeneously distributed. The solvent flows in the axial direction (z), and the extractor geometry

Fig. 3.5 A typical fixed bed extractor of the SFE process (z axial coordinate, H_B bed height)



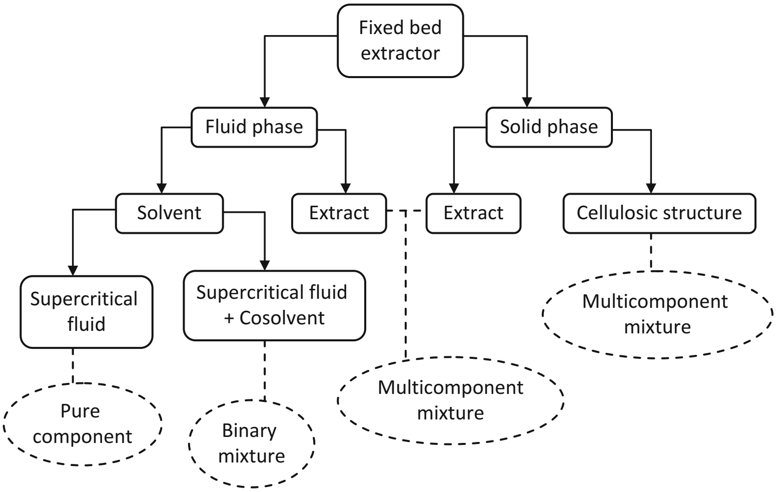


Fig. 3.6 Diagram of the fixed bed extractor composition in SFE from natural matrices

is such that the bed height can be considered infinitely larger than the bed diameter ($H_B >>> d_B$). Then, the terms of the radial (r) and tangential ($\ominus$) directions can be neglected in the mass balance equations. Moreover, the solid and fluid phases can be taken as nonreactive systems. By taking into account all of these assumptions, the mass balance in the extraction bed can be described by Eqs. 3.1 and 3.2 [14, 15]. It is interesting to note that in SFE, the fluid phase can be treated as a diluted solution; therefore, the solvent properties can replace the fluid-phase properties [10].

- *fluid phase*: [Accumulation] + [Convection] = [Dispersion] + [Interfacial Mass Transfer]

$$\frac{\partial Y}{\partial t} + u_i \frac{\partial Y}{\partial z} = \frac{\partial}{\partial z}\left(D_{aY}\frac{\partial Y}{\partial z}\right) + \frac{J\left(X, Y\right)}{\varepsilon} \tag{3.1}$$

- *solid phase*: [Accumulation] = [Diffusion] + [Interfacial Mass Transfer]

$$\frac{\partial X}{\partial t} = \frac{\partial}{\partial z}\left(D_{aX}\frac{\partial Y}{\partial z}\right) + \frac{J\left(X, Y\right)}{\left(1-\varepsilon\right)}\frac{\rho_{CO_2}}{\rho_S} \tag{3.2}$$

where Y is the mass ratio of the solute in the fluid phase (kg/kg), X is the mass ratio of the solute in the solid phase (kg/kg), t is the extraction time (s), u_i is the interstitial velocity of the solvent (m/s), z is the axial direction (m), D_{aY} is the dispersion coefficient in the fluid phase (m^2/s), D_{aX} is the diffusion coefficient in the solid phase (m^2/s), ρ_{CO2} is the solvent density (kg/m^3), ρ_S is the true density of the solid matrix (kg/m^3), $J(X,Y)$ is the interfacial mass transfer term (s^{-1}), and ε is the bed porosity (dimensionless).

The mass balance equations of the fluid and solid phases have been applied by several authors who have proposed many mathematical models based on the mass transfer phenomena that occur inside the extraction bed. One of the main differences among the proposed mathematical models is how each author describes the interfacial mass transfer term. This description depends on the personal assumptions that are made by each author when developing a different mass transfer model. Some of the mathematical models available in the literature are discussed in Sect. 3.7.

3.6.2 The Overall Extraction Curve (OEC)

According to Brunner [2], the course of SFE can be evaluated by analyzing the variables of (a) the total amount of extract, (b) the extraction rate, (c) the remaining amount of extract in the solid, and (d) the concentration of the extract in the supercritical solvent at the extractor outlet. All of the cited variables can be plotted as a function of the extraction time (or solvent consumption) to obtain curves that give important information regarding the SFE process. In most cases, variable (a) is selected such that the course of the extraction process is followed by determining the accumulated mass of the extract against the extraction time (or solvent consumption). This representation is the most commonly used and is well known as the *overall extraction curve* (OEC). The information provided by the OEC is useful for comparing the extraction results within a series of experiments when using the same solid matrix [2, 3].

The mass of the extract that accumulates during the SFE process is typically shaped as shown in the schematic curve presented in Fig. 3.7. The first part (*P–I*) of the curve is a straight line and, therefore, corresponds to a constant extraction

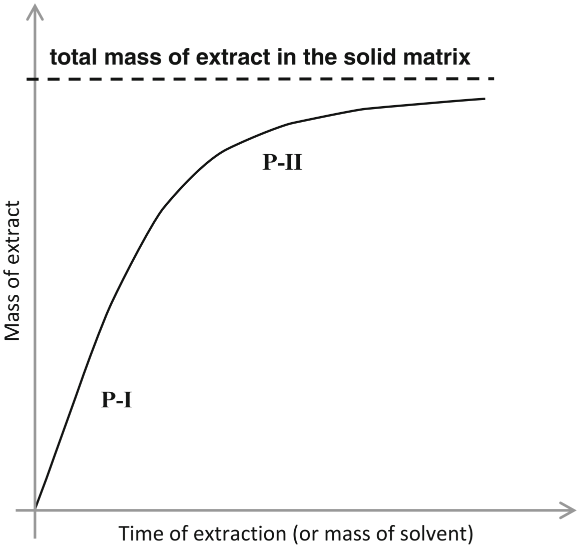


Fig. 3.7 The typical overall extraction curve (OEC) (*P-I* part 1, *P-II* part II) (Adapted from Brunner [2], with kind permission from Springer Science and Business Media)

rate period. The second part (P-II) is a nonlinear function that approaches a limiting value, that is, the total amount of extractable substances in the solid matrix [2]. Under certain processing conditions (as discussed in Sect. 3.5.1), the slope of the linear part of the graph may be given by the equilibrium solubility. However, it is fundamental to remember that the straight line generally occurs because the mass transfer resistance remains constant in the early stages of the extraction process. Therefore, the presence of the linear region is not a proof that equilibrium conditions have been attained during SFE [2, 3].

The shape of the OEC depends on the kinetics of solute extraction from the solid matrix and the solvation power of the SC-CO_2, which in turn depends on the operational conditions [3]. The course of the SFE from a solid matrix follows two types of curves for the extraction rate, as can be seen in Fig. 3.8. Curve 1 (C1) represents the extraction rate when a high initial concentration of solute in the solid substrate exists or when the solute is readily available to the solvent. Curve 2 (C2) represents the extraction rate when a low initial concentration of solute exists in the solid substrate or when the solute is not readily available to the solvent. Curve 2 also corresponds to the second part (P-II) of curve 1 because a depletion phase always comes after the first part (P-I, where a constant extract concentration is observed in the fluid phase at the outlet of the extraction cell) [2].

According to Brunner [2], the first part (P-I) of curve 1 (C1) has several main characteristics: (a) in the fluid phase, the mass transfer resistance dominates the process, (b) the solute compounds are readily available at the interface solid/fluid, and (c) a constant amount of extract is transferred to the bulk of the supercritical solvent, resulting in a constant concentration at the bed outlet. In the second part (P-II) of curve 1 (C1), as well as in curve 2 (C2), the extract concentration decreases with increasing extraction time due to the increasing mass transfer resistances and

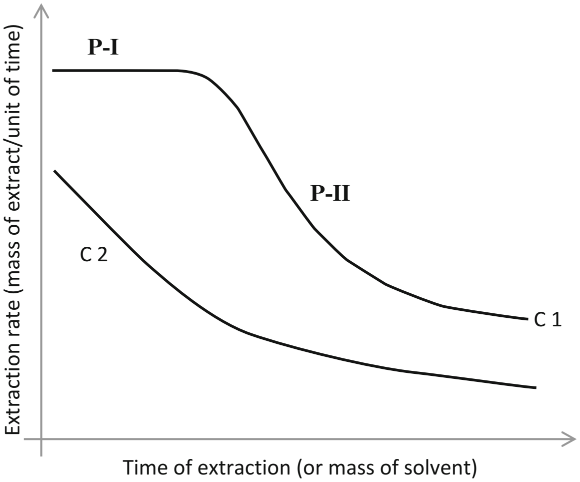


Fig. 3.8 Extraction rate curve: schematic illustration of curve 1 (C1) and curve 2 (C2) as described by Brunner [2] (the OEC from curve 1 has the shape previously presented in Fig. 3.7; *P-I* part 1, *P-II* part II) (Adapted from Brunner [2], with kind permission from Springer Science and Business Media)

the depletion of the extract in the solid phase. The solid matrix will be depleted of the extractable material in the direction of flow. The concentration of extract components increases in the direction of flow both in the SCF and in the solid material [2, 3].

3.7 Mathematical Modeling

Mathematical models based on the mass transfer phenomena, or even with merely empirical basis, are important tools in SFE investigations. The mathematical modeling of extraction curves may help develop an understanding of the kinetic behavior of SFE through the definition of extraction rates, steps, time, and/or mass transfer parameters with strong physical meaning [5]. The modeling of OECs helps the determination of the extraction time (cycle time), which is important for achieving the optimal utilization of an industrial-scale plant [2]. The main goal of using a mathematical model is the determination of parameters that may be applied to key aspects of process design, such as equipment dimensions, the solvent flow rate, particle size, and the solvent-to-feed (S/F) mass ratio, among others [16]. Thus, mathematical models can be useful tools for scale-up prediction, process design, and/or cost estimation purposes.

Knowledge of the initial distribution of a solute in the solid substrate directly affects the selection of the models that can adequately describe a given SFE system. The extractable substances may be distributed within the solid matrix in various ways. The solute can be (a) located freely on the surface of the solid material, (b) adsorbed on the outer surface of the solid material, (c) heterogeneously distributed inside the solid particle (located inside the pores or other specific cell structures), or (d) evenly distributed within the solid particles [17].

Many mathematical models have been developed to describe the OEC, ranging from simple equations to very complex equations. Some extensive reviews concerning the mathematical modeling of SFE were presented by Oliveira et al. [18] and Sovová [19], among other authors. In this chapter, it is not our intention to deliver a detailed discussion of all models available in the literature. Thus, we take a classical approach and focus on the fundamental concepts while presenting some well-known models from the SFE literature. According to Reverchon [17], the mathematical models used to describe the OEC can be divided into three main categories based on the approaches of (a) empirical evidence, (b) heat transfer analogy, or (c) differential mass balance integration.

The models developed from the first category are based on the hyperbolic shape of the typical OEC. One example is the model proposed by Esquível et al. [20] for describing the SFE of oil from olive husk. The empirical models use a hyperbolic function to fit the experimental data. The general form of the models from this category can be given by Eq. 3.3 [4]:

$$m_{\mathrm{EXT}} = X_0 F \left(\frac{t}{\mathrm{C}_1 + t} \right) \tag{3.3}$$

where m_{EXT} is the mass of the extract (kg), t is the time of extraction (s), F is the mass of the feed material (kg), X_0 is the initial mass ratio of the extractable solute in the solid substratum (kg/kg), and the constant C_1 is an adjustable parameter that has no physical meaning (s). The empirical model may give good fits in some particular cases, but it does not give any phenomenological information regarding the SFE process. Thus, this model has limited application in terms of scale-up and process design.

In the second category, an analogy is considered between SFE and the heat transfer by diffusion. In this case, all mass transfer is considered to happen based only on the mechanism of diffusion, allowing an apparent diffusion coefficient to be obtained [4]. The model presented by Crank [21] for the description of heat transfer in a solid particle cooling in a uniform medium was adapted by Reverchon [17] and was used to fit SFE data [15]. Reverchon [17] applied Fick's second law of diffusion to obtain a model that describes the OEC according to Eq. 3.4:

$$m_{\mathrm{EXT}} = X_0 F \left[1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(\frac{-n^2 \pi^2 D_{\mathrm{ef}} t}{r^2} \right) \right] \tag{3.4}$$

where m_{EXT} is the mass of the extract (kg); t is the time of extraction (s); F is the mass of the feed material (kg); X_0 is the initial mass ratio of the extractable solute in the solid substratum (kg/kg); n is an integer number; r is the radius of the spherical particle (m); and D_{ef} is the adjustable parameter, which represents the effective diffusion coefficient of the solute within the solid matrix (m^2/s). The application of the diffusion model is restricted to very few systems because in most cases, it results in a poor fit. This behavior is expected because mass transfer in SFE may not be properly described by diffusion alone because convective mass transport dominates the beginning of the process [4].

The third category comprises the majority of the mathematical models proposed for the description of SFE processes. The starting point is the evaluation of the differential mass balance (see Eqs. 3.1 and 3.2, which were presented in Sect. 3.6.1) inside the fixed bed extractor [4]. Then, each author gives a personal interpretation of the mass transfer phenomena that happen in both the fluid and solid phases. An example from this category is the model presented by Sovová [22], which has been extensively used by various researchers of SFE. A fundamental characteristic of this model is that the solute is distinguished in two different fractions, one present in broken cells and the other in intact cells [4]. As a result, this model was developed for application when the raw material passes through a milling process before extraction (see Sect. 3.3.1). The solute fraction present in the broken cells is denoted as the easily accessible solute (X_P), which is located at the particle surface and is the first fraction extracted. The fraction contained in the intact cells is denoted as the hardly accessible solute (X_K) and is located inside the solid particle. The OEC follows the shape of the type 1 curve (C1) described by Brunner [2] (as discussed in Sect. 3.6.2).

Sovová [22] divided the OEC into three distinguishable regions [10, 11] as follows:

- *Constant extraction rate (CER)*: In the CER period, the external surfaces of the solid particles are assumed to be fully covered with the easily accessible solute. In this region, the solute is essentially removed by convection; thus, the mass transfer resistance exists in the fluid phase.
- *Falling extraction rate (FER)*: In the FER period, flaws in the superficial solute layer begin to appear, and so the hardly accessible solute starts to be extracted. As a result, the solute is extracted by both convection and diffusion mechanisms. This is a transition period that is caused by the continuous depletion of the solute layer in the external surface.
- *Diffusion-controlled (DC)*: In the DC period, the solute at the particle surface is completely exhausted, and only the hardly accessible solute is available for extraction. As a result, mass transfer is controlled by intraparticle diffusion. The mass transfer resistance exists in the solid phase due to the low diffusivity of the solute in the solid matrix.

The model developed by Sovová [22] takes into account the solute solubility (Y^*) in the fluid phase and the mass transfer coefficients in both the fluid and solid phases (k_{YA} and k_{XA}, respectively) [10]. This model neglects the terms of dispersion and accumulation in the fluid phase, as well as the diffusion in the solid phase. Accumulation in the fluid phase was disregarded because the residence time of the solvent was considered to be low enough to support this assumption. Hence, the accumulation term was considered only in the solid phase [4]. The model also assumes pseudo-steady-state and plug flow. The parameters temperature, pressure, and solvent velocity are taken as constant throughout the entire extraction process. The fixed bed is assumed to be homogeneous with respect to the particle size and the initial solute distributions [10]. The mass balance equations proposed by Sovová [22] are presented in Eqs. 3.5 and 3.6 for the fluid and solid phases, respectively.

$$u_i \frac{\partial Y}{\partial z} = \frac{J\left(X, Y\right)}{\varepsilon} \tag{3.5}$$

$$\frac{\partial X}{\partial t} = \frac{J\left(X, Y\right)}{\left(1 - \varepsilon\right)} \frac{\rho_{CO_2}}{\rho_S} \tag{3.6}$$

where Y and X are the mass ratios of the solute in the fluid and solid phases, respectively (kg/kg); t is the extraction time (s); u_i is the interstitial velocity of the solvent (m/s); ρ_{CO2} and ρ_S are the solvent and solid matrix densities, respectively (kg/m^3); ε is the bed porosity (dimensionless); z is the axial direction (m); and $J(X,Y)$ is the interfacial mass transfer term (s^{-1}) as described by Eqs. 3.7 and 3.8, which must be applied when $X > X_K$ and $X \leq X_K$, respectively. The initial and boundary conditions for the mass balance equations are presented in Eqs. 3.9 and 3.10.

$$J\left(X, Y\right) = k_{YA}\left(Y^* - Y\right) \tag{3.7}$$

$$J\left(X, Y\right) = k_{XA} X \left(1 - \frac{Y}{Y^*}\right) \tag{3.8}$$

$$X\left(z, t = 0\right) = X_0 \tag{3.9}$$

$$Y\left(z = 0, t\right) = 0 \tag{3.10}$$

Sovová [22] solved the model equations and developed an analytical solution that is presented in Eqs. 3.11, 3.12, and 3.13, which must be applied, respectively, to the CER ($t \leq t_{\mathrm{CER}}$), FER ($t_{\mathrm{CER}} < t \leq t_{\mathrm{FER}}$), and DC regions ($t > t_{\mathrm{FER}}$). The extraction times that identify the ends of the CER and FER periods are denoted t_{CER} and t_{FER}, respectively.

$$m_{\mathrm{EXT}} = Q_{\mathrm{CO_2}} Y^* \left[1 - \exp\left(-Z\right)\right] t \tag{3.11}$$

$$m_{\mathrm{EXT}} = Q_{\mathrm{CO_2}} Y^* \left[1 - t_{\mathrm{CER}} \exp\left(Z_W - Z\right)\right] \tag{3.12}$$

$$m_{\mathrm{EXT}} = m_{SI} \left\{X_0 - \frac{Y^*}{W} \ln\left[1 + \exp\left(\frac{WX_0}{Y^*}\right) - 1\right] \exp\left[\frac{WQ_{\mathrm{CO_2}}}{m_{\mathrm{SI}}}\left(t_{\mathrm{CER}} - t\right)\right]\left(\frac{X_P}{X_0}\right)\right\} \tag{3.13}$$

Considering that

$$Z = \frac{m_{\mathrm{IS}} k_{\mathrm{YA}} \rho_{\mathrm{CO_2}}}{Q_{\mathrm{CO_2}}\left(1 - \varepsilon\right) \rho_S} \tag{3.14}$$

$$W = \frac{m_{\mathrm{IS}} k_{\mathrm{XA}}}{Q_{\mathrm{CO_2}} (1 - \varepsilon)} \tag{3.15}$$

$$Z_{\mathrm{W}} = \frac{Z Y^*}{W X_0} \ln \left\{ \frac{X_0 \exp\left[\frac{W Q_{\mathrm{CO_2}}}{m_{\mathrm{IS}}} (t_{\mathrm{CER}} - t) \right] - X_{\mathrm{K}}}{X_0 - X_{\mathrm{K}}} \right\} \tag{3.16}$$

$$t_{\mathrm{CER}} = \frac{m_{\mathrm{IS}} X_{\mathrm{P}}}{Y^* Z Q_{\mathrm{CO_2}}} \tag{3.17}$$

$$t_{\mathrm{FER}} = t_{\mathrm{CER}} + \frac{m_{\mathrm{IS}}}{Q_{\mathrm{CO_2}} W} \ln \left[\frac{X_{\mathrm{K}} + X_{\mathrm{P}} \exp\left({}^{W X_0} \big/ {}_{Y^*} \right)}{X_0} \right] \tag{3.18}$$

$$m_{\mathrm{IS}} = F - m_0 = F - (X_0 F) \tag{3.19}$$

The nomenclature used in Eqs. 3.11, 3.12, 3.13, 3.14, 3.15, 3.16, 3.17, 3.18, and 3.19 is specified as follows:

m_{EXT} = the mass of the extract (kg)
t = the extraction time (s)
F = the mass of the feed material (kg)
X_0 = the initial mass ratio of extractable solute in the solid substratum (kg/kg)
m_0 = the initial amount of extractable solute in the solid substratum (kg)
m_{IS} = the mass of the inert solid (kg)
Q_{CO2} = the solvent flow rate (kg/s)
ρ_{CO2} and ρ_{S} = the densities of CO_2 and the solid material, respectively (kg/m^3)
ε = the bed porosity (dimensionless)
Y^* = the solubility of the extract in the supercritical solvent (kg/kg)
X_{P} = the mass ratio of the easily accessible solute in the solid substratum (kg/kg)
X_{K} = the mass ratio of the hardly accessible solute in the solid substratum (kg/kg)
k_{YA} and k_{XA} = the mass transfer coefficients in the fluid and solid phases, respectively (s^{-1})

The application of the model developed by Sovová [22] generally results in good fits to experimental data for many different raw materials. A significant advantage of this model is that it provides a good physical description of the mass transfer phenomena in SFE processes [11]. Therefore, it is a convenient choice for the purposes of process design because the adjustable parameters (k_{YA}, k_{XA}, and X_{K}) can be applied in scale-up investigations. Years later, Sovová [23] presented another model that is also based on the concept of broken and intact cells. In this new model, the term for accumulation in the fluid phase was considered, and some changes were applied to the term of interfacial mass transfer. As a result, the complexity of the mathematical model increased significantly, and then the model was solved numerically because an analytical solution was no longer suitable [4, 23]. Furthermore, the number of adjustable parameters increased, and more information was required for the application of the new mathematical model, thereby limiting its practical use.

All of the models discussed thus far assume that the solute is a pseudocomponent. Martínez et al. [24] proposed a model that can be applied under two different assumptions regarding the solute composition, that is, to either a pseudocomponent or a multicomponent system. The assumption of a multicomponent system may be useful if there exists interest in knowing the kinetic behavior of specific compounds that are present in the extract. In this chapter, we present the model for a pseudocomponent solute, and we refer to it as the "logistic model." Further extension of this model to multicomponent systems is easily carried out because the same considerations and analogous equations are used.

According to Martínez et al. [24], the model begins by applying the differential mass balance inside the extraction bed for solid and fluid phases. This author neglected the terms of accumulation and dispersion in the fluid phase because he assumed that both phenomena lack significant influence relative to the convection term. The main peculiarity of this model is the definition of the term of interfacial mass transfer, which is described by one of the solutions from the logistic equation. The model equation for a pseudocomponent system is presented in Eq. 3.20. The logistic model has two adjustable parameters, named C_2 and t_m. No physical meaning is attributed to the first parameter (C_2), while the second (t_m) is defined as the time during which the extraction rate reaches its maximum value [24].

$$m_\mathrm{EXT} = \frac{X_0 F}{\exp\left(C_2 t_\mathrm{m}\right)} \left\{ \frac{1 + \exp\left(C_2 t_\mathrm{m}\right)}{1 + \exp\left[C_2\left(t_\mathrm{m} - 1\right)\right]} - 1 \right\} \tag{3.20}$$

where m_EXT is the mass of the extract (kg), t is the time of extraction (s), F is the mass of the feed material (kg), X_0 is the initial mass ratio of the extractable solute in the solid substratum (kg/kg), and C_2 (s^{-1}) and t_m (s) are the adjustable parameters.

The logistic model generally provides a relatively good fit to experimental data gleaned from different raw materials. However, when applying this model to common OEC shapes, many authors have obtained negative values for t_m; when this happens, no physical meaning can be attributed to the parameter t_m [13]. The absence of physical meaning brings an empirical character to this model; thus, the model has limited application in terms of process design and scale-up.

3.7.1 The Spline Model

Many different mathematical models have been used to describe and understand the kinetics of SFE processes, ranging from simple equations to very complex equations. An example of a simplified approach used to model the extraction curve is the so-called spline model, as presented by Meireles [9]. This model, which has an empirical basis, is based on the assumption that the OEC can be described by a family of N straight lines. The lines from the spline model can be calculated using Eq. 3.21 [9, 25][1] written for the 1st, 2nd, 3rd, …, and N-th lines:

$$m_{\mathrm{EXT}} = \left(b_0 - \sum_{i=1}^{i=N-1} t_i a_{i+1}\right) + \sum_{i=1}^{i=N} a_i t \tag{3.21}$$

where m_{EXT} is the mass of the extract (kg), t is the time of extraction (s), N is the number of straight lines, b_0 is the linear coefficient of line 1 (kg), $\sum a_i$ (for $i = 1$ to $i = N$) are the slopes of lines 1 to N (kg/s), and t_i (for $i = 1$ to $i = N-1$) is the time in which the intercept between line "i" and line "$i + 1$" occurs (s). Equation 3.21 is greatly simplified for two or three straight lines, as presented in Eqs. 3.22, 3.23, and 3.24. When considering an OEC described by 3 straight lines, the m_{EXT} for the three different periods of extraction should be calculated using the following equations [13]:

- For the first straight line ($t \leq t_1$), the m_{EXT} is obtained by Eq. 3.22:

$$m_{\mathrm{EXT}} = b_0 + a_1 t \tag{3.22}$$

- For the second straight line ($t_1 \leq t \leq t_2$), the m_{EXT} is obtained by Eq. 3.23:

$$m_{\mathrm{EXT}} = (b_0 - t_1 a_2) + (a_1 + a_2)\, t \tag{3.23}$$

- For the third straight line ($t \geq t_2$), the m_{EXT} is obtained by Eq. 3.24:

$$m_{\mathrm{EXT}} = (b_0 - t_1 a_2 - t_2 a_3) + (a_1 + a_2 + a_3)\, t \tag{3.24}$$

The spline model has been extensively used by our research group (LASEFI/FEA/UNICAMP) to model the kinetic data obtained from SFE studies [11, 13, 26–28]. This model has been applied based on considerations that the OEC can be described by two or three straight lines, depending on the shape of the extraction curve. Although the use of two straight lines may be adequate in some cases, the model with three lines is more versatile because it can be applied to any possible OEC shape. Moreover, when the OEC is described by three straight lines, it is possible to make a useful analogy with the three different extraction regions (the CER, FER, and DC periods, as previously discussed in Sect. 3.7) that are observed in a typical OEC. In this case, the parameters t_1 and t_2 (from Eqs. 3.23 and 3.24) correspond to t_{CER} and t_{FER}, the extraction times that mark the ends of the CER and FER periods, respectively. A schematic representation of an OEC that was fitted with three lines is presented in Fig. 3.9.

---

[1] The model presented here (Eq. 3.21) is the revised form of the equations previously published by Meireles [9, 25] because, in the original reference [9], typographical errors were present in the equation that describes the spline model.

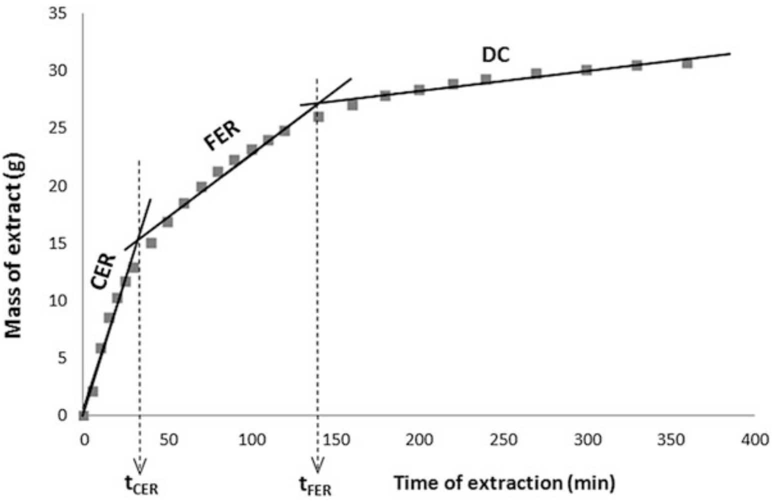


Fig. 3.9 Schematic representation of the spline model: extraction curve of SFE from clove bud (313 K/15 MPa, 226 g of feed material, solvent flow rate = 9.6×10^{-5} kg/s) fitted to three straight lines, which were prolonged to evidence the intercept points (t_{CER} and t_{FER}). Experimental data were obtained from Prado [27] (*CER* constant extraction rate, *FER* falling extraction rate, *DC* diffusion-controlled, t_{CER} is the time span of the CER period, t_{FER} is the time that marks the end of the FER period)

To fit the experimental OEC to a spline containing three straight lines, a nonlinear fit must be performed since the intercept points (t_{CER} and t_{FER}) are unknown. This can be carried out by using the procedures PROC REG and PROC NLIN of the SAS® software package (SAS Institute Inc., Cary, NC, USA) [13]. According to Jesus et al. [13], the fitted lines may be associated with three different mass transfer mechanisms (as illustrated in Fig. 3.9), following the classic description of the CER, FER, and DC periods [22]. Thus the first, second, and third lines can be related to the CER, FER, and DC regions, respectively. When studying SFE kinetics, it is a very common procedure to apply the spline model for the determination of various kinetic parameters that characterize the CER period. These parameters are [9, 13] the time span of the CER period (t_{CER}), the extraction rate of the CER period (M_{CER}), the mass ratio of the extract in the fluid phase at the bed outlet (Y_{CER}), the extraction yield of the CER period (R_{CER}), and the solvent-to-feed mass ratio of the CER period (S/F_{CER}). Both t_{CER} (s) and M_{CER} (kg extract/s) are adjustable parameters from the spline model (t_1 and a_1, respectively, as presented in Eq. 3.23). Y_{CER} (kg extract/kg CO_2) is obtained by dividing M_{CER} by the mean solvent flow rate (Q_{CO2}, kg CO_2/s). The parameters R_{CER} (%, kg extract/kg feed material) and S/F_{CER} (kg CO_2/kg feed material) should be calculated using modeled data (the values obtained for t_{CER} and m_{EXT} at the end of the CER period) [13].

The spline model generally presents a good fit to experimental data; thus, it is capable of delivering a good description of the OEC quantitative behavior [13]. Furthermore, although the model possesses an empirical basis and is comparatively simple in terms of its mathematical complexity, it nonetheless delivers helpful information regarding the SFE process. The association that can be made between the first line and the CER period is particularly useful because the CER region is the most important in terms of process design. According to Pereira and Meireles [7], between 50 and 90 % (w/w) of the total amount of extract can be recovered before the end of the CER period. Therefore, for many industrial applications, the extraction process may be ended shortly after t_{CER} because the best operational conditions are likely those in which a significant amount of extract is produced within a relatively short process time [7]. Therefore, the values of t_{CER} and R_{CER} approximately represent the minimum time that a SFE cycle should last and the minimum extraction yield expected under the given process conditions [9].

Some works on scale-up (see Sect. 3.8 for details) have demonstrated that the extraction yields and kinetic behaviors observed in laboratory assays can be reproduced on a pilot scale [16, 28–31]. Hence, it is possible that the same extraction yields may be achievable in an industrial plant. In this case, the parameters t_{CER}, $\mathrm{S/F_{CER}}$, and R_{CER} can be used in preliminary studies of economic feasibility (aspects concerned with cost estimation are discussed in Sect. 3.9). According to Leal [32], when using the spline model, the intersection between lines 1 and 3 (CER and DC, respectively, as illustrated in Fig. 3.9) defines an additional parameter of time, which is named t_{CER2}. This parameter can also be used as a good estimation of the process time in preliminary studies of COM predictions [13, 26].

In the literature on SFE, several additional complex mathematical models are presented for the description of the OEC. These models, which have a phenomenological basis, may provide reliable descriptions of the mass transfer mechanisms involved in the extraction process. This means that the adjustable parameters can have significant physical meanings and, as a result, may be used for scale-up purposes. Nonetheless, to apply phenomenological models, additional specific data are required. The model proposed by Sovová [22], for example, requires information concerning the extract solubility (Y^*) in supercritical CO_2, representing data that are not always available; in many cases, such data may not be available in the literature, and the associated experimental determination would be a difficult task (as discussed in Sect. 3.5.1). Thus, considering the difficulties encountered in finding specific data for many natural extracts, it is clear that one advantage of the spline model is that only kinetic data are necessary to carry out OEC mathematical modeling. Moreover, even with an empirical basis, this model provides useful and practical information concerning the SFE process, particularly with respect to the CER period.

3.8 Scale-Up

Scale-up is the task of achieving on a larger scale the same process behavior that was previously obtained in laboratory assays by considering the differences that are inherent to the processes conducted on equipment of significantly different sizes [5, 30]. By scaling up a process, a product with the same characteristics can ideally be obtained at a larger production rate with no or minimal modifications required. The prediction of a process behavior at the industrial scale is one of the most challenging tasks for food and chemical engineers [5].

After many decades of intensive research, the theoretical basis of SFE is now well established. Hundreds of publications concerning the optimization of process parameters in SFE from different raw materials are reported in published books, articles, and patents based on the results obtained on the laboratory scale. However, few data can be found for pilot-plant scales, and less data are available at the industrial scale [5]. Open and accessible knowledge regarding commercial-scale processes and equipment is very scarce. Information regarding industrial processes depends on the policies of the companies that use and sell SFE units [33].

The available scale-up data in the open literature are inconclusive, so there is no consensus regarding a general scale-up criterion that may be applicable to SFE from solid matrices [30]. To validate scale-up criteria, it is necessary to assess their applicability to different types of raw materials [34] because the mass transfer mechanisms depend on the specific characteristics of the solid substrates and respective solutes. The works that explore scale-up methods are usually limited to specific raw materials and process conditions; as a result, significant care is necessary when proposing a generalization. The process of defining universal scale-up criteria is very complex. However, when considering the main process parameters of SFE and how they affect extraction yield and kinetics, it may be possible to find ways of achieving some effective scale-up procedures [5].

In SFE, the scale-up objective is the reproduction of the same extraction curve at a larger scale by preserving some of the extraction parameters used at the laboratory scale. Therefore, the biggest challenge is the discovery of which parameters, when conserved, will lead to the same results (extraction rates, yields, and chemical compositions of the products) when performing the scale-up procedure. The solution to this type of problem is tricky, and the challenge involves deep knowledge of the limiting factors of the SFE process, which may be based on either thermodynamics or mass transfer [5]. Del Valle et al. [35] suggested that caution is required when working with simple scale-up procedures because in SFE, the relationships between extraction rates and extraction conditions depend on several parameters and may be very complex. Moreover, differences between the mass transfer phenomena may occur when significantly increasing the process scale [35]. However, Prado et al. [30] emphasize that the use of some simple criteria could help the development of easily applicable scale-up methods, which would decrease the time and cost utilized in the design of a SFE process.

According to Clavier and Perrut [36], a simple scale-up procedure for SFE processes can be conducted by following two main steps: (a) perform small-scale experiments to define the optimal extraction conditions by scanning over the operational parameters (different pressures, temperatures, solvent-to-feed ratios, and others) and then (b) select the scale-up method based on the factors that limit mass transfer during extraction. Depending on the complexity and kinetic limitations of the process, different strategies may be applied to the design of the production unit. The easiest scale-up method consists of holding one or both of the ratios of Q_{CO2}/F and S/F constant, where Q_{CO2} is the solvent flow rate, F is the feed mass in the extractor, and S is the solvent mass required for the extraction [36]. Then, three scale-up criteria can be proposed [36]: (a) in the case of an extraction limited by solubility, the S/F ratio should be held constant between the small and large scales; (b) for a process limited by internal diffusion, the Q_{CO2}/F ratio should be conserved from the small to the large scale; and (c) when both diffusion and solubility are limiting mechanisms, both ratios (S/F and Q_{CO2}/F) should be held constant in the scale-up process.

The Q_{CO2}/F ratio is inversely proportional to the residence time of the solvent inside the extractor, as can be seen in Eq. 3.25. It is important to emphasize that the solvent density (ρ_{CO2}), the bed porosity (ε), and the bed apparent density (ρ_{B}) should be preserved when studying the abovementioned scale-up criteria. Therefore, it is clear that the residence time (t_{RES}) will be conserved if the ratio between the solvent flow rate (Q_{CO2}) and the feed mass in the extractor (F) is held constant. Clavier and Perrut [36] note that the contact time between the solvent and solid matrix is a determining factor for processes limited by internal diffusion; as a result, the residence time should be conserved from the small to the large scale.

$$t_{\mathrm{RES}} = \frac{\varepsilon \rho_{\mathrm{CO2}} F}{\rho_B Q_{\mathrm{CO2}}} \tag{3.25}$$

where t_{RES} is the residence time of the solvent (s), ε is the bed porosity (dimensionless), ρ_{CO2} is the solvent density (kg/m^3), ρ_{B} is the bed apparent density (kg/m^3), F is the feed mass in the extractor (kg), and Q_{CO2} is the solvent flow rate (kg/s).

The criterion that necessitates maintaining the Q_{CO2}/F ratio as a constant (and consequently preserving the residence time) has been effective when applied to the scale-up of SFE from clove [16], peach almond [31], and striped weakfish wastes [37]. However, it is considered unsatisfactory for the scale-up of SFE data from vetiver roots [16]. This may have resulted from the physical properties of vetiver oil (particularly, its high viscosity), which could have affected the mass transport properties in small-scale experiments and may have contributed to a significant loss of the extract at some locations within the equipment [16]. In the just-mentioned works [16, 31, 37], the large-scale experiments were conducted on SFE equipment with capacities no larger than 300 cm^3; hence, no assays were performed on pilot-scale units. The same criterion (constant Q_{CO2}/F) was used to investigate the scale-up of SFE from red pepper by performing large-scale experiments in a pilot-plant unit [5]. The authors observed that the extraction curves obtained at the laboratory (300 cm^3 capacity) and pilot (5,150 cm^3 capacity) scales exhibited significantly different kinetic behaviors, so the applied scale-up criterion could not be used to accomplish the authors' goal [5]. According to Martínez and Silva [5], the divergences observed between applications at small and large scales may have occurred as a result of bed compaction, variations in the efficiencies during the separation step, distinct bed geometries, and mechanical dragging. Martínez et al. [16] also investigated another scale-up proposal that consisted of holding constant the superficial velocity of the solvent; however, this criterion was ineffective because the results obtained for large-scale experiments were far from those achieved for small-scale experiments.

In recent works from our research group, the criterion based on holding constant both the *S*/*F* and Q_{CO2}/F ratios has been successfully applied to the scale-up of SFE from different raw materials [27–30]. In these works, the small-scale extraction curves were obtained on laboratory-scale equipment (an extraction vessel measuring 290 cm^3 in volume) and were then used as references for scaling up the SFE process. The large-scale experiments were performed in a pilot-plant unit (an extraction vessel measuring 5,150 cm^3 in volume), containing three separators that were arranged in series. The proposed criterion was effective for the scale-up data of SFE from clove [30], sugarcane residue [30], grape seeds [28], ginger [27], and annatto seeds [29]. Taking into account the feed mass in the extractor, a 15-fold scale-up was achieved for clove and sugarcane residue [30], a 17-fold scale-up was performed for grape seeds [28] and ginger [27], and a 12-fold scale-up was accomplished for annatto seeds [29]. The extraction curves obtained in small- and large-scale experiments had similar shapes, but in all cases, the authors found that the pilot-scale yields were higher (ranging from 5 to 20 % higher, depending on the raw material used) than those achieved in the small-scale assays [27–30]. According to Prado et al. [30], the manufacturers of SFE equipment claim that the extraction process is more efficient at larger scales, so the higher yields achieved in pilot-scale experiments are in agreement with the information delivered by manufacturers.

The scale-up procedure suggested by Clavier and Perrut [36] (holding one or both of the *S*/*F* and Q_{CO2}/F ratios constant) provides the significant advantage of simplicity. Nonetheless, this approach does not take into account several important factors that may affect the extraction process (radial diffusion, axial mixing, bed compaction, etc.) and is incapable of predicting the effects of using a series of extractors. A refined scale-up method that integrates all of the relevant factors in SFE processes requires a numerical simulation that may estimate any possible plant configuration and may lead to the optimization of industrial units [36].

3.9 Economic Analysis

It is apparent that industries must earn profits, so even the most brilliant technology will never be accepted unless it can provide a product with a price tag that is at least compatible to that of similar products that are already available in the market [38]. This means that demonstrating the economic feasibility of an emerging technology is the only way to attract potential investors. Therefore, researchers should blend their scientific enthusiasm with economic awareness [38] because the cost aspects are fundamental to the process design.

According to Meireles [9], SFE from solid matrices was shown to be a technically feasible process. However, despite the increasing number of industrial plants in operation all over the world, in many regions (e.g., Latin America), SFE is not applied on a commercial scale [9]. Thus, although SFE has been used as an industrial operation since the 1980s [2], it can still be considered an emerging technology because the conventional techniques continue to be the most commonly used approaches in various applications of solid-fluid extraction. One reason for this is the restraints imposed by the high investment costs, which are usually associated with the high-pressure aspect of the processes [9, 39]. Therefore, to spread SFE technology, it is critical to find ways of demonstrating that this technique can be profitable. Indeed, this is a task of major importance with respect to preventing the elimination of SFE at the very early stages of the process design. Hence, efforts must be undertaken to develop simple and reliable methods for estimating the cost of manufacturing (COM) of SFE products because cost information is a determinant factor in the initial stages of business plan analyses [9, 40]. Moreover, it is also important to emphasize that a preliminary analysis of the COM must be performed with minimal experimental information [40].

The COM of various SFE extracts has been systematically studied by our research group for more than a decade. Based on the knowledge acquired from this systematic investigation, we can state that the following information must be available to perform cost estimations:

- The *operating conditions of temperature and pressure* should be selected by taking into account the results from GYI experiments (see Sect. 3.5.2). Both parameters are strongly related to equipment specifications and the utilities demand.
- The *extraction yield for a given extraction time and solvent-to-feed ratio*, which are process parameters that should be obtained from the OEC (see Sect. 3.6.2). These parameters are necessary to determine the rates of solvent consumption and extract production, as well as the cycle time.
- The *description of the raw material pretreatment*, which are the process steps that must be conducted prior to the extraction process (as discussed in Sect. 3.3.1). The pretreatment requirements are important for estimating the preprocessing costs.
- The *bed apparent density* is required to calculate the mass of feed material that must be packed into a certain bed volume. If a given production rate is desired, then the plant capacity and the raw material demand can be determined using the bed apparent density.
- The *extract composition* is valuable information, although it is not necessary when calculating the COM. Nonetheless, characterization of the extract, in terms of its chemical compounds and functional properties, is essential information for defining the selling price of SFE products. If a reliable estimation of the selling price can be made, then it is possible to also make a good prediction of the payback period, which is a cost parameter that may attract investors and aid decision makers.

Rosa and Meireles [39] presented a simple procedure for estimating the COM of extracts obtained by SFE. These authors applied the methodology described by Turton et al. [41], in which the COM is calculated as a sum of the direct costs, fixed costs, and general expenses [9, 39]. The direct costs are directly dependent on the production rate, that is, they are composed of the costs of raw materials, operating labor, and utilities, among others. The fixed costs are independent of the production rate and involve taxes, insurance, depreciation, etc. The general expenses are associated with business maintenance, such as administrative costs, research and development, and sales expenses, among others [39]. The three components of the COM (direct costs + fixed costs + general expenses) are then estimated in terms of five main costs, as expressed in the model (Eq. 3.26) proposed by Turton et al. [39, 41]:

$$\mathrm{COM} = 0.304F_{\mathrm{CI}} + 2.73C_{\mathrm{OL}} + 1.23\left(C_{\mathrm{UT}} + C_{\mathrm{WT}} + C_{\mathrm{RM}}\right) \tag{3.26}$$

where COM is the cost of manufacturing, which is expressed in US$/kg; F_{CI} is the fixed cost of investment; C_{OL} is the cost of the operating labor; C_{UT} is the cost of the utilities; C_{WT} is the cost of waste treatment; and C_{RM} is the cost of the raw materials.

The fixed cost of investment (F_{CI}) can be calculated on a yearly basis as the product of the total investment by the annual depreciation rate (normally, a 10 % rate is considered). In addition to the expenses associated with equipment and installations, the investment cost should also include the initial amount of CO_2 that is required to fill the solvent reservoir [39]. The cost of operational labor (C_{OL}) is related to the number of workers that are needed to operate the process equipment (extractors, separators, heat exchangers, compressors, pumps, storage tanks, etc.). The cost of the utilities (C_{UT}) is calculated by considering the demand for heating steam, cooling water, and electric power [26, 39].

In the SFE of natural products, the raw material is a plant or animal substrate, which may require one or more pretreatment steps (cleaning, selection, drying, milling, etc.) before extraction can be performed. The cost of the raw materials (C_{RM}) is composed of expenses that include the solid substrate (both the solid matrix and all of the pretreatment costs) and the loss of CO_2 during the process. The solvent lost is associated with the leaking of CO_2 from the system, either as a result of dissolution in the extract after the separation process or entrapment in the solid substrate that is removed from the extractor [39]. Rosa and Meireles [39] considered that a factor of 2 % (taking into account the total amount of solvent used in a cycle of extraction) was adequate for estimating the CO_2 lost. Regarding the generation of waste, the only waste accumulated is the exhausted solid, which is harmless and can be reused in other industrial applications or is simply disposed of as an ordinary organic waste [26]. In particular cases, the exhausted solid is the main desired product, as in the removal of caffeine from coffee, the reduction of nicotine in tobacco, and the removal of cholesterol from foods, among others. Therefore, the cost of waste treatment (C_{WT}) can be completely neglected and is assumed to be zero [26, 39].

As long as the production requirements of a particular SFE process are known, the optimal configuration of the industrial plant can be determined [36]. A typical SFE unit (see Fig. 3.1) is composed of two or more extraction columns; two or more separators (flash tanks), which are arranged in series to allow a certain degree of extract fractionation; a CO_2 reservoir; a solvent pump; heat exchangers; a compressor for CO_2 recycling; several valves; and temperature and pressure controllers [7, 39].

To determine the input and output mass rates and the energy demands of the industrial process, the mass and energy balance equations must be solved. This can be achieved by using software (either homemade or commercial packages) that addresses process engineering calculations. In recent years, our research group has adopted the commercial software SuperPro Designer® (Intelligent Inc., Scotch Plains, NJ, USA) as a useful tool for studying the economic feasibility of SFE [26, 28, 34, 42–46]. This software allows calculations of the process and economic parameters, so it can be used to perform simulations of industrial-scale processes. The COM and the payback period are some of the output data obtained from simulations performed in SuperPro Designer®. According to the Association for the Advancement of Cost Engineering International, cost estimations can be divided into five classes (1–5), which are defined by taking into account the degree of accuracy between the predicted value and the real COM. The class 5 estimation is based on the lowest level of project definition, while the class 1 estimation is closer to the final definition of the industrial project. The SuperPro Designer® software is capable of estimating COMs that may be classified as classes 2–3 [26].

It is well known that the COM of a SFE product is significantly influenced by extraction time (t_{EXT}), which is the time required for one cycle of extraction. Therefore, it is very important to know the extraction curve because kinetic data can be used to estimate the time in which the COM reaches its minimum value. Prado et al. [28] studied the economic viability of the production of grape seed oil by SFE. These authors investigated different times of extraction (from 60 to 300 min) and plant capacities (0.005, 0.05, and 0.5 m^3). The minimum COM (12 US$/kg) was found for a plant size of 0.5 m^3 by considering an extraction time equal to 240 min [28]. Taking into account the selling price (40–80 US$/kg) of a similar product (grape seed oil obtained by cold pressing), the SFE process was considered to be economically viable [28]. Other examples of recent works in which similar cost analyses were performed are summarized in Table 3.1.

The economic feasibility of a SFE product depends on a comparative analysis between COM and the product's selling price [9, 28, 39]. If the preliminary COM estimated for a certain extract is lower than the market price of a similar product, then there is a very strong indication that the process under investigation can be economically viable. However, defining a selling price may not be a trivial task because SFE extracts are still innovative products. Therefore, in many situations, an equivalent product is not yet available in the market, preventing a selling price from being accurately determined. Moreover, in the natural products market, the prices are directly dependent on the extract quality, which can be evaluated in terms of its chemical composition and functional properties. Then, depending on the composition and properties of the extract, different selling prices are possible. It is well established that, in most cases, SFE extracts tend to possess quality advantages compared to extracts obtained by other techniques, particularly in comparison to extracts produced with low-pressure solvent techniques. This happens because

Table 3.1 Cost of manufacturing (COM) of extracts obtained by supercritical fluid extraction (SFE)

Raw material	Botanic name	Target compounds	T (K)	P (MPa)	t_{EXT} (min)	S/F (kg/kg)	Yield (%)	COM (US$/kg)	Selling price (US$/kg)	Ref.
Clove buds	*Eugenia caryophyllus*	Volatile oil	313	15	52	3.65	14.2	31	100	[45]
Grape seeds	*Vitis vinifera*	Unsaturated fatty acids and antioxidants	313	35	240	6.6	9.9	12	40–80	[28]
Annatto seeds	*Bixa orellana*	Tocotrienols	313	20	105	8.7	2.75	115	NI	[29]
Cashew leaves	*Anacardium occidentale*	Volatile oil, flavonoids, alkaloids, and antioxidant compounds	318	20^{a}	47	11.5	1	24	NI	[42]
Lemon verbena leaves	*Aloysia triphylla*	Volatile oil and flavonoids	333	35	180	9.1	1.8	1070	1375	[34]
Mango leaves	*Mangifera indica*	Variety of bioactive compounds (flavonoids, alkaloids, terpenes, terpenoids, and antioxidant compounds)	323	30	90	4.2	1.8^{b}	92	10–500	[46]

T temperature, P pressure, t_{EXT} extraction time, S/F solvent-to-feed ratio, *NI* not informed, *Ref.* reference

[a] SFE was performed using ethanol (5 %) as a cosolvent

[b] Approximated value (obtained by visual observation of the overall extraction curve)

SFE is a green, selective, and mild extraction method, resulting in an extract that is enriched in desirable compounds, free of toxic solvents, and without the loss of compounds due to thermal degradation or oxidative reactions [7]. Thus, SFE products may be given higher prices in comparison to extracts obtained using other extraction methods. Prado and Meireles [45] reported that the selling price of clove oil extracted by SFE is 110 US$/kg, whereas the price of clove volatile oil obtained by steam distillation varies between 26 and 86 US$/kg. Generally, when the SFE product is still not available in the market, the selling prices of oils produced by steam distillation or cold pressing may be used as initial references in the cost analyses of oils obtained by SFE [28, 39, 45].

In some cases, a preliminary cost analysis can indicate that the COM of a SFE extract is too close to or even higher than the market price of a similar product [39, 44]. Even so, it is important to bear in mind that certain considerations must be made before disregarding SFE as a viable process [39]. Some of the important factors that should be considered when evaluating the results obtained in a preliminary cost analysis are listed below [39, 44, 46]:

- *Optimization of the process parameters*: Generally, further and detailed studies of process parameters can result in significant cost reductions. If the extraction rates are increased, then the extraction time and the COM will be reduced [45]. Additionally, the evaluation of different plant configurations and operating modes (by varying the number and arrangement of extractors) may lead to increasing productivity, which can lead to a decrease in the operating costs and COM [3, 6].
- *Different selling prices*: The prices of natural products can vary significantly according to the concentration of one or more target compounds. Extracts obtained by SFE are generally recognized as nutraceutical products; as a result, they may possess special uses and distinct prices. Therefore, the amount and availability of specific bioactive compounds should be carefully evaluated to verify the quality of the product and to specify the market price of the extract [39].
- *Scale increase*: Many authors have demonstrated that the COM of a SFE product tends to be reduced when the plant capacity is increased [26, 28, 34, 42, 45, 46]. Albuquerque and Meireles [26] reported that the COM (SFE extract obtained from annatto seeds) decreased from 125 to 109 US$/kg as the extraction vessels' capacities were increased from 0.1 to 0.5 m^3.
- *Advancements in project detailing*: In a preliminary analysis, the COM tends to be overestimated because the worst-case scenarios are normally assumed to avoid cost underestimations. Uncertainties in the process design are diminished as the project advances, allowing more accurate cost calculations to be performed.

It is common knowledge that high-pressure plants are associated with high investment costs. However, the cost of SFE units has decreased in recent years due to competition between suppliers, which has motivated significant technical improvements and cost reductions [44]. Furthermore, it is important to emphasize that the COM is calculated as a sum of five main costs (as previously presented in Eq. 3.26) [39]; hence, several other cost aspects (not only the investment costs) must be considered to evaluate the economic feasibility of SFE processes. Many recent works have reported that SFE can be an economically viable method for obtaining bioactive extracts [28, 29, 34, 39, 45]. Thus, it is clear that a promising business opportunity is available [9] because SFE has shown true potential as a profitable alternative for the production of high-quality and high value-added products.

References

1. Rostagno MA, Prado JM (eds) (2013) Natural product extraction: principles and applications. The Royal Society of Chemistry, Cambridge
2. Brunner G (1994) Gas extraction: an introduction to fundamentals of supercritical fluids and the application to separation processes. Steinkopff, Darmstadt
3. Brunner G (2005) Supercritical fluids: technology and application to food processing. J Food Eng 67(1–2):21–33. http://dx.doi.org/10.1016/j.jfoodeng.2004.05.060
4. Rosa PTV, Meireles MAA (2009) Fundamentals of supercritical extraction from solid matrices. In: Meireles MAA (ed) Extracting bioactive compounds for food products: theory and application. CRC Press/Taylor & Francis Group, Boca Raton, pp 272–288
5. Martínez J, Silva LPS (2013) Scale-up of extraction processes. In: Rostagno MA, Prado JM (eds) Natural product extraction: principles and applications. The Royal Society of Chemistry, Cambridge, pp 363–398
6. Moraes MN, Zabot GL, Meireles MAA (2013) Assembling of a supercritical fluid extraction equipment to operate in continuous mode. In: Proceedings of the III Iberoamerican conference on supercritical fluids, Cartagena de Indias, 1–5 April 2013
7. Pereira CG, Meireles MAA (2010) Supercritical fluid extraction of bioactive compounds: fundamentals, applications and economic perspectives. Food Bioprocess Technol 3(3):340–372. http://dx.doi.org/10.1007/s11947-009-0263-2
8. Rodrigues VM, Sousa EMBD, Monteiro AR, Chiavone-Filho O, Marques MOM, Meireles MAA (2002) Determination of the solubility of extracts from vegetable raw material in pressurized CO_2: a pseudo-ternary mixture formed by cellulosic structure + solute + solvent. J Supercrit Fluids 22(1):21–36. http://dx.doi.org/10.1016/S0896-8446(01)00108-5
9. Meireles MAA (2008) Extraction of bioactive compounds from Latin American plants. In: Martinez JL (ed) Supercritical fluid extraction of nutraceuticals and bioactive compounds. CRC Press/Taylor & Francis Group, Boca Raton, pp 243–274
10. Ferreira SRS, Meireles MAA (2002) Modeling the supercritical fluid extraction of black pepper (*Piper nigrum* L.) essential oil. J Food Eng 54(4):263–269. http://dx.doi.org/10.1016/S0260-8774(01)00212-6
11. Sousa EM, Chiavone-Filho O, Moreno MT, Silva DN, Marques MOM, Meireles MAA (2002) Experimental results for the extraction of essential oil from *Lippia sidoides* Cham. using pressurized carbon dioxide. Braz J Chem Eng 19(2):229–241. http://dx.doi.org/10.1590/S0104-66322002000200003
12. Carvalho RN Jr, Moura LS, Rosa PTV, Meireles MAA (2005) Supercritical fluid extraction from rosemary (*Rosmarinus officinalis*): kinetic data, extract's global yield, composition, and antioxidant activity. J Supercrit Fluids 35(3):197–204. http://dx.doi.org/10.1016/j.supflu.2005.01.009
13. Jesus SP, Calheiros MN, Hense H, Meireles MAA (2013) A simplified model to describe the kinetic behavior of supercritical fluid extraction from a rice bran oil byproduct. Food Public Health 3(4):215–222. http://dx.doi.org/10.5923/j.fph.20130304.05
14. Vasconcellos CMC (2007) Extração supercrítica dos óleos voláteis de *Achyrocline satureioides* (Macela) e *Vetiveria zizaioides* (Vetiver): determinação da cinética de extração e estimativa de custos de manufatura. UNICAMP (University of Campinas), Brazil

15. Martínez J (2005) Extração de óleos voláteis e outros compostos com CO_2 supercrítico: desenvolvimento de uma metodologia de aumento de escala a partir da modelagem matemática do processo e avaliação dos extratos obtidos. UNICAMP (University of Campinas), Brazil
16. Martínez J, Rosa PTV, Meireles MAA (2007) Extraction of clove and vetiver oils with supercritical carbon dioxide: modeling and simulation. Open Chem Eng J 1(1):1–7
17. Reverchon E, Marrone C (1997) Supercritical extraction of clove bud essential oil: isolation and mathematical modeling. Chem Eng Sci 52(20):3421–3428. http://dx.doi.org/10.1016/S0009-2509(97)00172-3
18. Oliveira ELG, Silvestre AJD, Silva CM (2011) Review of kinetic models for supercritical fluid extraction. Chem Eng Res Des 89(7):1104–1117. http://dx.doi.org/10.1016/j.cherd.2010.10.025
19. Sovová H (2012) Modeling the supercritical fluid extraction of essential oils from plant materials. J Chromatogr A 1250:27–33. http://dx.doi.org/10.1016/j.chroma.2012.05.014
20. Esquível MM, Bernardo-Gil MG, King MB (1999) Mathematical models for supercritical extraction of olive husk oil. J Supercrit Fluids 16(1):43–58. http://dx.doi.org/10.1016/S0896-8446(99)00014-5
21. Crank J (1975) The mathematics of diffusion, 2nd edn. Oxford University Press, Oxford
22. Sovová H (1994) Rate of the vegetable oil extraction with supercritical CO_2—I. Modelling of extraction curves. Chem Eng Sci 49(3):409–414. http://dx.doi.org/10.1016/0009-2509(94)87012-8
23. Sovová H (2005) Mathematical model for supercritical fluid extraction of natural products and extraction curve evaluation. J Supercrit Fluids 33(1):35–52. http://dx.doi.org/10.1016/j.supflu.2004.03.005
24. Martínez J, Monteiro AR, Rosa PT, Marques MO, Meireles MAA (2003) Multicomponent model to describe extraction of ginger oleoresin with supercritical carbon dioxide. Ind Eng Chem Res 42(5):1057–1063. http://dx.doi.org/10.1021/ie020694f
25. Meireles MAA (2013) Supercritical CO_2 extraction of bioactive components from algae. In: Domínguez H (ed) Functional ingredients from algae for foods and nutraceuticals. Woodhead Publishing, Cambridge, pp 561–584
26. Albuquerque CLC, Meireles MAA (2012) Defatting of annatto seeds using supercritical carbon dioxide as a pretreatment for the production of bixin: experimental, modeling and economic evaluation of the process. J Supercrit Fluids 66:86–95. http://dx.doi.org/10.1016/j.supflu.2012.01.004
27. Prado JM (2010) Estudo do aumento de escala do processo de extração supercrítica em leito fixo. UNICAMP (University of Campinas), Brazil
28. Prado JM, Dalmolin I, Carareto NDD, Basso RC, Meirelles AJA, Vladimir Oliveira J, Batista EAC, Meireles MAA (2012) Supercritical fluid extraction of grape seed: process scale-up, extract chemical composition and economic evaluation. J Food Eng 109(2):249–257. http://dx.doi.org/10.1016/j.jfoodeng.2011.10.007
29. Albuquerque CLC (2013) Obtenção de sementes desengorduradas e de óleo rico em tocotrienóis de urucum por extração supercrítica: estudo dos parâmetros de processo, do aumento de escala e da viabilidade econômica. UNICAMP (University of Campinas), Brazil
30. Prado JM, Prado GHC, Meireles MAA (2011) Scale-up study of supercritical fluid extraction process for clove and sugarcane residue. J Supercrit Fluids 56(3):231–237. http://dx.doi.org/10.1016/j.supflu.2010.10.036
31. Mezzomo N, Martínez J, Ferreira SRS (2009) Supercritical fluid extraction of peach (*Prunus persica*) almond oil: kinetics, mathematical modeling and scale-up. J Supercrit Fluids 51(1):10–16. http://dx.doi.org/10.1016/j.supflu.2009.07.008
32. Leal PF (2008) Estudo comparativo entre os custos de manufatura e as propriedades funcionais de óleos voláteis obtidos por extração supercrítica e destilação por arraste a vapor. UNICAMP (University of Campinas), Brazil
33. Brunner G (2010) Applications of supercritical fluids. Annu Rev Chem Biomol Eng 1:321–342. http://dx.doi.org/10.1146/annurev-chembioeng-073009-101311

34. Prado JM, Veggi PC, Meireles MAA (2014) Supercritical fluid extraction of lemon verbena (*Aloysia triphylla*): process kinetics and scale-up, extract chemical composition and antioxidant activity, and economic evaluation. Sep Sci Technol 49(4):569–579. http://dx.doi.org/10.1080/01496395.2013.862278
35. del Valle JM, Rivera O, Mattea M, Ruetsch L, Daghero J, Flores A (2004) Supercritical CO_2 processing of pretreated rosehip seeds: effect of process scale on oil extraction kinetics. J Supercrit Fluids 31(2):159–174. http://dx.doi.org/10.1016/j.supflu.2003.11.005
36. Clavier J-Y, Perrut M (2004) Scale-up issues for supercritical fluid processing in compliance with GMP. In: York P, Kompella UB, Shekunov BY (eds) Supercritical fluid technology for drug product development. Marcel Dekker, New York, pp 565–601
37. Aguiar AC, Visentainer JV, Martínez J (2012) Extraction from striped weakfish (*Cynoscion striatus*) wastes with pressurized CO_2: global yield, composition, kinetics and cost estimation. J Supercrit Fluids 71:1–10. http://dx.doi.org/10.1016/j.supflu.2012.07.005
38. Prasad NK (2012) Downstream process technology: a new horizon in biotechnology. PHI Learning Private Limited, New Delhi
39. Rosa PTV, Meireles MAA (2005) Rapid estimation of the manufacturing cost of extracts obtained by supercritical fluid extraction. J Food Eng 67(1–2):235–240. http://dx.doi.org/10.1016/j.jfoodeng.2004.05.064
40. Meireles MAA (2003) Supercritical extraction from solid: process design data (2001–2003). Curr Opinion Solid State Mater Sci 7(4–5):321–330. http://dx.doi.org/10.1016/j.cossms.2003.10.008
41. Turton R, Ballie RC, Whiting WB, Shaeiwitz JA (1998) Analysis, synthesis, and design of chemical process. Prentice Hall PTR, Upper Saddle River
42. Leitão NCMCS, Prado GHC, Veggi PC, Meireles MAA, Pereira CG (2013) *Anacardium occidentale* L. leaves extraction via SFE: global yields, extraction kinetics, mathematical modeling and economic evaluation. J Supercrit Fluids 78(0):114–123
43. Prado IM, Albuquerque CLC, Cavalcanti RN, Meireles MAA (2009) Use of a commercial process simulator to estimate the cost of manufacturing (COM) of carotenoids obtained via supercritical technology from palm and buriti trees. In: Proceedings of the 9th international symposium on supercritical fluids, Arcachon, 18–20 May 2009
44. Prado JM, Assis AR, Maróstica-Júnior MR, Meireles MAA (2010) Manufacturing cost of supercritical-extracted oils and carotenoids from Amazonian plants. J Food Process Eng 33(2):348–369. http://dx.doi.org/10.1111/j.1745-4530.2008.00279.x
45. Prado JM, Meireles MAA (2011) Estimation of manufacturing cost of clove (*Eugenia caryophyllus*) extracts obtained by supercritical fluid extraction using a commercial simulator. In: Proceedings of the 11th international congress on engineering and food, Atenas, 22–26 May 2011
46. Prado IM, Prado GHC, Prado JM, Meireles MAA (2013) Supercritical CO_2 and low-pressure solvent extraction of mango (*Mangifera indica*) leaves: global yield, extraction kinetics, chemical composition and cost of manufacturing. Food Bioprod Process 91(4):656–664. http://dx.doi.org/10.1016/j.fbp.2013.05.007