



Supercritical Extraction of Flavonoid Compounds from *Dorema aucheri* Boiss. Experimental and Modeling Using CH₂Cl₂ as Co-Solvent

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In recent years there is an increasing interest to replace chemically synthesized compounds by natural equivalents that can be found mostly in plant materials. *Dorema aucheri* Boiss. is a native Iranian plant, which has medicinal properties. In this work the extraction of flavonoid compounds from this plant, with supercritical carbon dioxide, is studied. A mathematical two phase model is developed to simulate extraction yield at different operating conditions (pressure, temperature, void bed fraction and dynamic extraction time). Results indicated that these parameters had significant effect on the extraction yield. After analyzing the extracted products by GC and GC/MS, α -eudesmol (39.2 %) and δ -cadinene (12.9 %) were the major bioactive flavonoid compounds in this plant. The optimum pressure, temperature, void bed fraction and dynamic extraction time were 21 MPa, 318 K, 0.28 and 1 h, respectively. The present findings showed, supercritical extraction is a promising and alternative process for recovering the flavonoid compounds from *Dorema aucheri* with high concentration.

Key Words: *Dorema aucheri*, Medicinal plants, Antioxidant, Bioactive compounds.

INTRODUCTION

Iran is one of the countries, has the largest medicinal plants with traditional agriculture. *Dorema aucheri* Boiss. (Apiaceae) is an umbelliferae species in the flora of Iran, full of flavonoid compounds. Flavonoids are a kind of highly effective antioxidant. These compounds are a kind of highly effective natural antioxidant that control the blood cholesterol and triglyceride and used especially in kidney problems. Although this plant is used more traditionally there is less study about its physiological property and the best way of its extraction. Supercritical fluid extraction (SFE) is a new and powerful developing technique in separation process that produces bioactive compounds by pure technology, under mild conditions. Carbon dioxide is the most widely used solvent in supercritical fluid extraction, since it is physiologically harmless, environmentally safe, non-explosive, and readily available and it can be easily removed from products. Nowadays, supercritical fluid extraction, is widely used as an attractive alternative extraction method to conventional liquid extraction in wide variety areas including the industries of food, pharmacy and environmental engineering, chemical and oil industries^{1,2}. From an engineering point of view, the scale-up of supercritical fluid extraction units requires both the knowledge of the

relevant process parameters such as equilibrium and mass transfer kinetics, and also the optimum operating conditions³. These parameters may be obtained by using an accurate mathematical description of the extraction process and experimental laboratory data. To reduce the complexity of the model it is also necessary to make simplifying assumptions about how the solute is distributed inside the solid adsorbed in pore network, tied inside cell structures or homogeneously distributed inside particles and about the mechanisms involved in the mass transfer, kinetics internal mass transfer resistance, external mass transfer resistance or a combination of various resistances³. Optimization of the experimental conditions is a critical step in the development of a successful supercritical fluid extraction process due to the effect of various variables on the extraction efficiency³⁻⁷. The objectives of the present study were to investigate the effect of several supercritical fluid extraction parameters (pressure, temperature, void bed and dynamic extraction time) on the supercritical CO₂ extraction of flavonoid compounds from *Dorema aucheri*.

EXPERIMENTAL

The plant was used in this study named *Dorema aucheri* (Apiaceae) with the herbarium No. of AR337E that was collected close to the city of Yasuj in Iran (North 30°, 19.644' and

East 51°, 44.885°). Air dried *Dorema aucheri* was grounded in a blender to produce a fine powder with some average particle sizes. Dichloromethane with certified purity of 99.9 % was provided by Merck Co., Germany. The CO₂ used in this study with purity higher than 99.9 %, obtained from Erlich gas Co., Iran.

Characterization of the *Dorema aucheri* fixed bed: The fixed bed was formed with 5 g of *Dorema aucheri*, which have been milled in the desired size, added to the extractor in small portions. Care was taken to obtain a uniform bed avoiding wall effects and channeling.

Experimental procedure: The experiments were carried out in a bench scale apparatus. Carbon dioxide is feed from a tank gas and liquefied by a condenser, then a pump is used to put the liquefied carbon dioxide under the needed pressure through a surge tank. The surge tank and vessel has been designed in form of a shell and tube. So that warm water is circulated in its shell with constant temperature. Prior to the extraction, the material is usually grinded to increase the surface area in contact with the supercritical solvent and also increase the accessibility of the solute inside cell structures, thus increasing mass transfer kinetics. This enables the description of the resulting particles using the basic geometries of slab, cylinder or sphere. For this study, about 5 g of dried *Dorema aucheri* and glass beads were loaded in high pressure vessel with internal volume 250 mL. Glass beads prevent channeling of the flow in packed beds and the dead volume. The static time in this study is 45 min, after the static time the dynamic conditions started by entering the supercritical-CO₂ to the cell and opening the outlet back pressure valve. The product was collected in a U-tube separator. The outlet was immersed in dichloromethane and the temperature of the solvent was kept at below 0 °C using ice and salt both during dynamic extraction time. Then CO₂ goes from a gas meter. Fig. 1 shows the schematic diagram of the extractor apparatus.

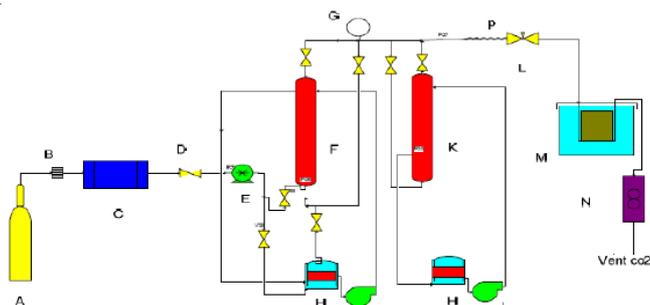


Fig. 1. Schematic diagram of the extraction of flavonoids from *Dorema aucheri* plant with supercritical carbon dioxide: A: CO₂ tank; C: condenser; D: check valve; E: pump; F: surge tank; G: pressure gauge; H: warm baths; I: Water pump; K: extraction column; L: restrictor valve; M: sample collection vessel; N: gas meter; P: Temperature controlled restrictor valve

Model description: The overall extraction rate from *Dorema aucheri* can be mathematically described by a set of partial differential equations (PDEs). The following major assumptions must be made to derive the governing differential equations: 1. Solid particles are spherical, monosized, for small particles it was assumed that particle solute concentration is independent of radius and is a function of time only (lumped

system). 2. Temperature and pressure are uniform across all regions of the extractor so the system is isothermal and isobaric. 3. The radial concentration gradients in the extractor are neglected so axial dispersion is significant. 4. Although several components are present in the extract, their mass-transfer behavior is assumed to be similar and is described as a single pseudo-component. 5. There is local equilibrium at the interface of the fluid and solid phases and the equilibrium relationship is linear. 6. The volume fraction of the extractor is not affected by the reduction of the solid mass during extraction. In other words, the solids do not change their volume during the extraction process. It means bed void fraction and particle porosity doesn't change during extraction. 7. The physical properties of the solvent do not change during extraction. 8. The solvent velocity pattern is that of plug flow and assumed to be constant across the extractor. Applying conservation of mass, the following equation can be written for element (Fig. 2)^{7,8}.

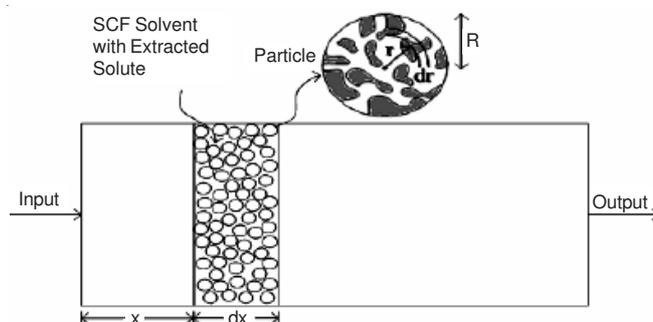


Fig. 2. Schematic representation of element in supercritical fluid extraction rig.

$$\frac{\partial Y_b}{\partial \eta} + a \frac{\partial Y_b}{\partial X} = \frac{a}{P_c} \frac{\partial^2 Y_b}{\partial X^2} - 3 \left(\frac{1 - \epsilon_b}{\epsilon_b} \right) \text{Bi} (Y_b - Y_{p,R,p}) \quad (1)$$

That

$$Y_b = \frac{C}{C_{p,0}} \quad X = \frac{x}{L} \quad a = \frac{u \cdot R_p^2}{L \cdot D_{\text{eff}}} \quad P_c = \frac{u \cdot L}{D_{\text{ax}}}$$

The boundary and initial conditions for this equation are:
Initial condition (IC): $\eta = 0 \rightarrow Y_b = 0$ (2)

$$\text{B.C.1: } X = 0 \rightarrow \frac{D_{\text{ax}}}{L} \frac{\partial Y_b}{\partial X} = u Y_b \rightarrow Y_b - \frac{D_{\text{ax}}}{uL} \frac{\partial Y_b}{\partial X} = 0 \rightarrow Y_b - \frac{1}{P_c} \frac{\partial Y_b}{\partial X} = 0 \quad (3)$$

$$\text{Boundary condition (BC2): } X = 1 \rightarrow \frac{\partial Y_b}{\partial X} = 0 \quad (4)$$

For large particle element is inside the particle but for small particles element is considered to be at surface of particle because small particle can be considered as lumped system.

Applying mass balance for small particle will result in eqn. 5:

$$\frac{dc_s}{dt} = -3 \frac{k_f}{R_p} (C_s - C) \quad (5)$$

The initial condition of this equation is:

$$@ t = 0 \rightarrow C_s = C_{s0} \quad (6)$$

Applying mass balance for large particle will result in eqn. 7:

$$\varepsilon_p \frac{\partial Y_p}{\partial \eta} + (1 - \varepsilon_p) b \frac{\partial Q}{\partial \eta} = \frac{1}{\xi^2} \frac{\partial}{\partial \xi} \left(\xi^2 \frac{\partial Y_p}{\partial \xi} \right) \quad (7)$$

The relevant boundary and initial conditions are:

$$\begin{cases} \eta = 0 \rightarrow Y_p = 1 \\ \eta = 0 \rightarrow Q = 1 \end{cases} \quad (8)$$

$$@\xi = 0 \Rightarrow \frac{\partial(Y_p C_{p0})}{\partial(\xi R_p)} = 0 \Rightarrow \frac{\partial Y_p}{\partial \xi} = 0 \quad (9)$$

$$\begin{aligned} @\xi = 0 \Rightarrow -D_{\text{def}} \frac{\partial(Y_p C_{p0})}{\partial(\xi R_p)} &= k_f (Y_{p,Rpl} C_{pl} - Y_b C_{p0}) \Rightarrow \\ \frac{\partial Y_p}{\partial \xi} &= \text{Bi}(Y_p - Y_{p,Rp}) \end{aligned} \quad (10)$$

By applying conservative of mass law for whole extractor system, extraction yield can be described as following:

Extraction yield (Y) = (Mass of extracted / total mass of solute in *Dorema aucheri* leaves) × 100

$$\frac{dY}{d\tau} = \frac{LA\varepsilon}{n_0} C/X = 1 \quad (11)$$

The initial condition of this equation is:

$$@\tau = 0 \rightarrow F = 0 \quad (12)$$

For small particle solved eqns. (1), (5) and (11) simultaneously, but for large particle solved eqns. (1), (7) and (11) simultaneously.

Solution technique: In order to solve partial differential equations (PDEs) finite difference method has been implemented^{9,10}. The length of bed was dividing into 'm' section, the radius of the small particles was divided into '1' part and 'n' parts for large particles ['P' equals to 'm+(i-1)n'] then the partial differential equations were expanded by finite difference methods. Equations (1) and (7) may be solved using a linear equilibrium relationship between concentrations in the solid phase and supercritical fluid extraction phase at the interface, where q and Cs are related by assuming an equilibrium condition as follows:

$$q = K C_s \quad (13)$$

Equilibrium constant should be determined so the model data must fit with experimental data. On the other hand the value of K is obtained by the sum of the squares of the difference between the experimental extraction yield and the predicted extraction yield, that must be minimized. The criterion is described by eqn. (14) as:

$$\text{OBJ} = \sum (Y_{\text{model}} - Y_{\text{exp}})^2 \quad (14)$$

In this case a value for K was guessed, then solved the model and OBJ was calculated for constant velocity data only (small scale and constant residence time data use for test the model)^{7,11,12}. Operation stops if the value of OBJ is lower than a specified small number otherwise the procedure continues. Therefore, there are three eqs. which can be solved, simultaneously.

Model parameters: The parameters involved in this model are mass transfer coefficient to the bulk phase and axial

dispersion coefficient in the supercritical phase. Critical temperature, critical pressure, acentric factor and average molecular weight of extract were obtained from Takeuchi equation. The density of CO₂ was calculated using the Soava/Redlich/Kwong equation of state¹⁰. The effective intra particle diffusion coefficient of supercritical fluid extraction extract was estimated^{2,13,14} to be $D_e = D_m \cdot \varepsilon_p^2$. The axial dispersion coefficient in the SC phase was approximated as follows¹⁵:

$$Pe_{pd} = 1.63 Re^{0.265} Sc^{-0.919} \quad (15)$$

where,

$$D_L = \frac{U_0 d_p}{Pe_{pd} \varepsilon} \quad (16)$$

The physical properties of the solvent at experimental conditions are shown in Table-1. As well, model parameters were optimized by minimizing the error between experimental data and predicted yield of the model, by Nelder-Mead simplex method using MATLAB 7.1 software. The mass transfer coefficient in an SC extractor was estimated using the empirical correlation.

$$Sh = 0.38 Re^{0.83} Sc^{1/3} \quad (17)$$

where,

$$k_f = \frac{Sh D_e}{2R} \quad (18)$$

which, is valid over Re range from 2 to 40 and Sc from 2 to 40. The external diffusivity is about $1 \times 10^{-8} \text{ m}^2/\text{s}$ for such systems in the temperature and pressure ranges of 40-50 °C and 160-200 bar, respectively^{16,17}. The same value of external diffusivity is assumed in this study. Viscosity of supercritical CO₂ was estimated using Jossi empirical correlation:

$$\begin{aligned} [(\mu - \mu^*) \xi^* + 10^{-4}]^{1/4} &= 0.10230 + 0.023364 \rho_r \\ &+ 0.058533 \rho_r^2 - 0.040758 \rho_r^3 + 0.0093324 \rho_r^4 \end{aligned} \quad (19)$$

In eqn. (19) the value of ξ^* for CO₂ is 0.0224. Furthermore, μ^* which is the viscosity in the normal pressure (0.1-5 bar) can be calculated as follows:

$$\mu^* \xi^* = 34.0 \times 10^{-5} T_r^{0.94}, T_r \leq 1.50 \quad (19a)$$

$$\mu^* \xi^* = 17.78 \times 10^{-5} (4.58 T_r - 1.67)^{5/8}, T_r > 1.50 \quad (19b)$$

RESULTS AND DISCUSSION

The yield of flavonoids by mathematical modeling and experiments are presented in Figs. 3-5. In these figures, sharp variation of the yield is observed at initial period of extraction because at the static condition, some flavonoids are extracted and gathered at the outer surface of the particles. Solutes in the outer parts of particles are extracted much faster than the solutes in the inner parts of particles at the beginning of the dynamic extraction. As the extraction time proceeds, the diffusion of solutes from inner parts to the bulk phase becomes more difficult due to the decrease in driving force between the solid and fluid phases leading to the reduction of extraction rate. It has been proven that the optimum extraction pressure and temperature for obtaining high yield of flavonoids resulting in negligible solubility of the other components are in the

ranges from 170 to 200 bar and from 40 to 50 °C^{18,19}. Also the range of process parameters such as pressure, temperature and void bed fraction are given in Table-1. As shown in Figs. 3-5 the mean Y value of these runs was determined 58.34 by *t*-test method using 97 % confidence level. The estimated error of ± 1.32 for the mean value of 58.34 confirms the precision of the experiments and their significant differences at different conditions. Also the mass transfer parameters and K values are reported in Table-1. This table shows a decrease in k_f with increasing pressure or decreasing temperature although enhances the D_{ax} . An increase in void bed fraction may cause an increase in mass transfer area in contact with solvent; therefore, leading to a higher k_f . Moreover, it causes a decrease in Reynolds number and leading to reduce Peclet number, thereby the D_{ax} is increased. However, variation in void bed fraction does not influence the K. Modification of the extraction process conditions can cause to reduce the K, which leads to extraction enhancement from solid into the pores and reduce the internal mass transfer resistance. Consequently, it is important to optimize the conditions to reduce the internal resistance and improve the yield.

P(MPa)/ T(K)/ ϵ_b	ρ (Kg ^m ⁻³)	μ (*10 ⁵ Kgm ⁻¹ s ⁻¹)	k_f (*10 ⁵ m ² s ⁻¹)	D_{ax} (×10 ¹³ m ² s ⁻¹)	k
15/318/0.28	775	6.95	4.12	2.71	0.189
17/318/0.28	795	7.10	2.73	2.93	0.183
19/318/0.28	805	7.50	1.52	3.20	0.177
21/318/0.28	825	7.65	0.83	3.46	0.173
23/318/0.28	840	8.00	0.721	3.81	0.171
19/313/0.28	820	8.30	1.321	4.75	0.128
19/323/0.28	845	7.15	1.11	3.08	0.184
19/318/0.18	805	7.50	1.273	3.05	0.181
19/318/0.38	805	7.50	1.414	3.73	0.178

Table-2 depicts, the oil of *D. aucheri* at each temperature and pressure, consists of eight monoterpene hydrocarbons (*ca.* 5.3 %), three oxygenated monoterpenes (*ca.* 4 %), 15 sesquiterpene hydrocarbons (*ca.* 37 %), 6 oxygenated sesquiterpenes (*ca.* 35.6 %) and three aliphatic compounds (*ca.* 7.3 %). α -Eudesmol (39.2 %) and δ -cadinene (12.9 %) were the major compounds in this oil.

Pressure (Mpa)	15	17	19	21	23	19	19	19	19
Temperature (°K)	318	318	318	318	318	313	323	318	318
Void bed	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.18	0.38
Compound									
α -Pinene	0.63	0.68	0.76	0.8	0.82	0.74	0.68	0.68	0.77
Camphene	0.12	0.16	0.15	0.2	0.20	0.17	0.15	0.14	0.18
β -Pinene	0.14	0.17	0.17	0.2	0.18	0.17	0.16	0.15	0.16
Myrcene	0.18	0.21	0.31	0.3	0.28	0.26	0.25	0.26	0.27
Limonene	0.40	0.90	1.20	1.4	1.32	1.28	1.24	1.18	1.21
(E) β -Ocimene	0.30	0.44	0.56	0.6	0.51	0.40	0.38	0.36	0.42
γ -Terpinene	0.11	0.17	0.23	0.3	0.28	0.27	0.26	0.25	0.28
Terpinolene	0.70	0.90	0.90	1.0	0.87	0.76	0.65	0.53	0.64
Thymol-methyl ether	0.12	0.11	0.22	0.2	0.19	0.21	0.28	0.11	0.14
Bornyl acetate	0.14	0.06	0.14	0.2	0.18	0.17	0.18	0.20	0.20
Methyl geranate	1.70	1.90	2.80	3.6	3.10	3.21	3.43	3.21	3.48
α -Cubebene	0.07	0.06	0.08	0.1	0.08	0.07	0.064	0.091	0.10
α -Copaene	1.00	1.30	1.90	2.1	1.50	1.60	1.76	1.97	2.09
β -Patchoulene	0.11	0.20	0.28	0.3	0.27	0.19	0.21	0.28	0.29
β -Caryophyllene	1.20	2.50	3.70	3.9	3.10	3.20	3.40	3.60	3.60
α -Santalene	1.20	1.34	1.67	1.5	1.12	1.23	1.43	1.49	1.50
b-Gurjunene	1.12	1.30	2.00	2.2	1.90	2.00	2.10	2.30	2.48
Aromadendrene	0.21	0.30	0.48	0.5	0.34	0.40	0.43	0.46	0.50
α -Humulene	0.16	0.12	0.17	0.2	0.17	0.18	0.186	0.19	0.12
Germacrene D	0.45	0.67	0.76	0.8	0.73	0.68	0.54	0.30	0.76
β -Selinene	2.00	2.20	2.20	2.3	2.10	2.00	1.97	1.80	1.90
Viridiflorene	2.80	3.20	3.27	3.3	3.15	3.10	2.90	2.67	2.80
γ -Cadinene	11.7	11.9	12.76	12.9	11.18	11.1	11.0	10.87	11.2
δ -Cadinene	1.70	1.87	2.23	2.2	2.10	2.00	1.80	1.67	2.00
Cadina-1,4-diene	0.13	0.18	0.18	0.2	0.16	0.15	0.21	0.19	0.20
Germacrene B	2.90	2.87	3.00	3.3	3.10	3.30	3.40	3.00	2.90
Germacrene D-4-ol	0.18	0.25	0.29	0.3	0.27	0.26	0.20	0.29	0.27
<i>trans</i> -Sesquisabinene hydrate	0.48	0.53	0.67	0.6	0.50	0.46	0.39	0.44	0.57
Hexadecan	1.78	1.90	2.00	1.2	1.00	1.10	1.14	1.19	1.22
2-Pentadecanone	2.90	3.10	3.45	3.9	3.20	3.40	3.10	2.96	3.10
γ -Eudesmol	0.18	0.19	0.19	0.2	0.16	0.15	0.14	0.13	0.12
Cubenol	0.46	0.54	0.59	0.6	0.54	0.63	0.48	0.43	0.44
α -Eudesmol	37.12	38.4	39.00	39.2	38.12	37.0	36.5	39.1	39.00
α -Cadinol	1.92	2.02	2.10	2.2	2.00	2.12	2.00	2.12	2.40
Hexadecanoic acid	0.16	0.18	0.21	0.2	0.18	0.16	0.20	0.23	0.19

Effect of pressure: As shown in Fig. 3, the cumulative yield of flavonoids *versus* dynamic time is plotted in five different pressures at constant temperature and void bed fraction, which are compared with experimental results. It is observed that increasing pressure improves the yield, up to 21 MPa, whereas Y decreases by further increasing the pressure (at 23 MPa). Such a change of Y *versus* pressure is due to dual effect. On one hand, adding the pressure causes higher supercritical-CO₂ density, therefore improves the solubility of flavonoids and leads to higher Y. On the other hand, increasing pressure reduces the supercritical-CO₂ diffusivity then resulting to lower Y. The results reveal that at the higher pressures more than 21 MPa the effect of low diffusivity is dominant and the Y is reduced.

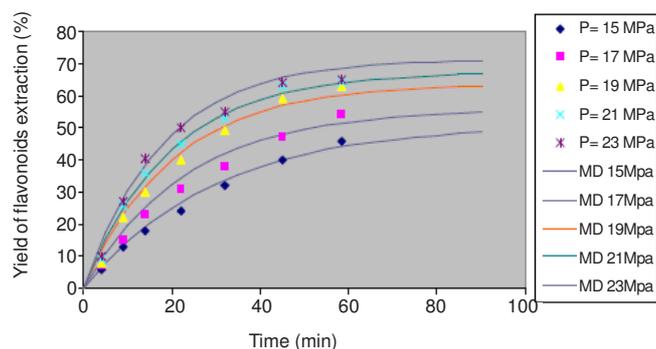


Fig. 3. Effect of pressure on the extraction yield at T=318 K and $\epsilon_b = 0.28$

Effect of temperature: Fig. 4 shows the effect of temperature on Y at pressure of 19 MPa and void bed fraction of 0.28. Like the pressure, temperature displays a nonlinear and complex effect on the extraction near or above the critical point. Increasing the temperature, decreases the supercritical-CO₂ density. While higher temperature (323 K) lowers down the yield. Fig. 4 shows that the inverse effect of temperature begins around 323 K in this process.

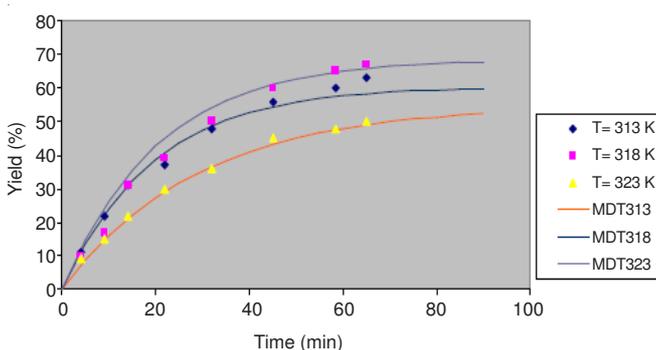


Fig. 4. Effect of temperature on the extraction yield at P = 20 MPa and $\epsilon_b = 0.28$

Effect of void bed: Besides pressure and temperature, the void bed fraction has an impact on the extraction efficiency. Data presented in Fig. 5 show the effect of void bed on Y. When the void bed fraction is 0.38, the Y after a 58.3 min extraction time is about 68.98%, while in the void bed fraction of 0.18, the Y reduces to 60.57 % after the same extraction period (under pressure of 19 MPa and temperature of 323 K).

Greater void bed can enlarge the contact area between solvent and solid; hence it can improve the mass transfer of oil to the supercritical CO₂, although from the economic point of view, the fewer void bed is more suitable.

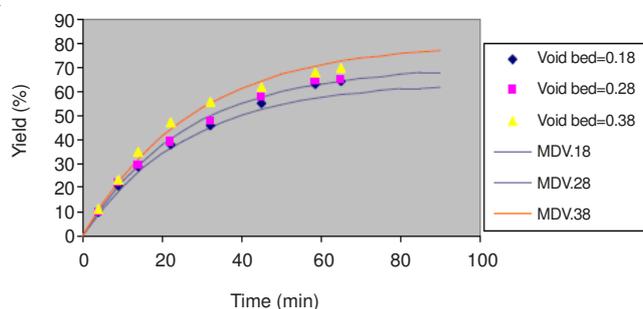


Fig. 5. Effect of void bed on extraction yield at T=318 K and P = 20 MPa

Effect of dynamic extraction time: Figs. 3-5 show the effect of dynamic time on the extraction yield of *Dorema aucheri* leaves in supercritical-CO₂ with applying several different pressures, temperatures and void bed faraction levels. At each figures, the extraction yield is increased with dynamic time until 90 min. It can be concluded that the solvent power of supercritical CO₂ density is reduced due to the lower CO₂ density and maximum yield was obtained at 90 min. However, at higher pressures (23 MPa) the extraction rate is higher and as a consequence the extraction yield kept increasing but after 60 min of extraction time, the extraction yield dropped (Figs. 3-5), the highest extraction yield was achieved at 1 h dynamic time.

Conclusion

High recovery of flavonoid compounds from *Dorema aucheri* leaves can be obtained by using supercritical carbon dioxide extraction. For simulation of this extraction, a model proposed and the equilibrium constant between solid and supercritical fluid was determined. In addition the equilibrium constant reported as a function of temperature and pressure which decreases with pressure and increases with temperature and the effect of temperature, pressure and bed void fraction on extraction yield were investigated. This model was solved with numerical techniques and the results were compared with experimental data. This comparison has been shown that the proposed model is in good agreement with experimental data. According to the results, the optimal conditions were found to be at 21 MPa, 318 K, and 0.28 void bed fraction. The greatest effect on the extraction yield and selectivity of the extraction was observed from temperature, after that followed by pressure and dynamic extraction time. It was shown that *Dorema aucheri* is a potential source of flavonoid compounds. So supercritical fluid technology is now considered to be an innovative and promising way to design and modify pharmaceutical substances. This method allows for easy removal of the solvent by depressurization and control of extraction condition by variation of temperature, pressure or time.

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