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CO-SOLVENT SELECTION FOR TOCOTRIENOL EXTRACTION FROM PALM FATTY ACID DISTILLATE USING SUPERCRITICAL CARBON DIOXIDE

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ABSTRACT

A predictive model was devised for the estimation of the Kamlet-Taft (KT) dipolarity/polarisability (π) parameter for binary mixtures of supercritical carbon dioxide (scCO_2) and co-solvent. The model allows the selection of the best co-solvent for the extraction of tocotrienols from palm fatty acid distillate (PFAD). Ethanol, acetone, and isopropanol were separately used as co-solvents in the range of 0.05 - 0.15 mL/g for the experimental set-up at 20 MPa and 53°C for 300 min and a CO_2 flow rate of 32 ± 5 g/min. The model's estimations of π* for all these binary mixtures followed the trends for the extraction of tocotrienols. The π* values increased with the concentration of co-solvent in the binary system and tocotrienol extraction was directly proportional to the π* value, but only up to a particular value. Of the three co-solvents tested, ethanol was predicted to be the best to enhance tocotrienol extraction. With a 0.075 mL/g of ethanol, the extraction yield was $30.03^a \pm 0.03$ mg/g, more than that achieved with pure scCO_2 ($16.45^b \pm 2.02$ mg/g).*

Keywords: co-solvents, Kamlet-Taft, palm fatty acid distillate, supercritical fluid extraction, tocotrienols.

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INTRODUCTION

Agricultural by-products are essential sources of natural antioxidants. Palm fatty acid distillate (PFAD) is a by-product of refining crude palm oil. While PFAD is commonly used as a fatty acid for non-food industries, it is also a source of various bioactive compounds for the food and health industries, such as tocopherols, tocotrienols, squalene, sterols and others.

Both tocopherols and tocotrienols belong to the vitamin E family and are components of palm oil (Colombo, 2010). Tocotrienols have more excellent neuroprotective, anticancer, and cholesterol-lowering effects than tocopherols (Colombo, 2010). They exist as four different isomers: α-, β-, γ- and δ-tocotrienol. All except β-tocotrienol exhibit more incredible health benefits than α-tocopherol. Colombo (2010) reported that a nanomolar concentration of α-tocotrienol could prevent neurodegeneration.

Supercritical carbon dioxide (scCO_2) extraction has been extensively used to extract bioactive compounds and lipids (Brunner, 2005). The development of scCO_2 technology is in line with the environmental sustainability issues. Efficient extraction of scCO_2 is due to the low viscosity, density, and high diffusivity of scCO_2 to interact with the solute in the sample. Altering the main operating conditions of the scCO_2 system, such as pressure and temperature, will directly impact the physical properties, including the density of scCO_2. For instance, increasing pressure at a constant temperature will increase the solvent's density and solvating power. Thus, the consideration of the density at the supercritical region is necessary since the pressure and temperature of scCO_2 significantly impact it.

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Nevertheless, $scCO_2$ is a nonpolar solvent with high selectivity for nonpolar to moderately polar compounds. This makes $scCO_2$ less efficient for the extraction of high polarity compounds. The addition of co-solvents (modifiers or entrainers) in the $scCO_2$ system improves extraction and fractionation, especially in food and pharmaceutical applications. Sato *et al.* (2017) reported that using a co-solvent resulted in a higher yield of compounds such as saccharides and cinnamic acid, which also have antioxidant properties. Jafarian *et al.* (2020) reported an increase in the amount of phytosterol (67% by weight) extracted from rapeseed oil deodoriser distillates through the addition of 5% (v/v) ethanol to the $scCO_2$ process at 35 MPa and 313 K. Lima *et al.* (2019) reported that the addition of methanol (5% v/v) to the $scCO_2$ process enhanced the yield of oil extracted from *Piper klotzschianum* leaves to approximately 40%. De O Silva *et al.* (2019) demonstrated the $scCO_2$ extraction of oil from pomegranate seeds with alcohol (ethanol, methanol, or isopropanol) as a co-solvent that produces speciality oils rich in conjugated linolenic acid, phenolics and tocopherols.

Polar co-solvents are commonly used in the $scCO_2$ extraction process, at concentrations of 5%-20%, to increase the solubility of the compounds of interest, reducing the main operating condition such as pressure and carbon dioxide (CO_2) consumption, hence, increasing the separation process (Duereh *et al.*, 2020b; Tirado *et al.*, 2019). Co-solvents can modify the characteristics of the supercritical solvent, such as its polarity. Technically, CO_2 has a non-specific interaction with the solute of interest, via dispersion. The presence of a co-solvent can improve the extraction process by creating a specific interaction with polar solutes, via hydrogen bonding. Nevertheless, a greater understanding of the actions of a co-solvent is necessary to optimise the extraction of the compounds of interest.

Extraction of palm oil waste under supercritical conditions has been conducted either by using co-solvent or without the aid of co-solvent. However, a full investigation on estimating the effect of co-solvent on the tocotrienols extract from PFAD using the predictive model of Kamlet-Taft (KT) Dipolarity/Polarisability has been partially reported. The KT parameters provide detailed information on a solvent's characteristics, particularly its modes of action and solubility (Islam *et al.*, 2020). In this regard, KT solvatochromic dipolarity/polarisability (π^*) can predict the effect of a solvent on the separation of a target compound; hence, knowledge of this parameter enables the best co-solvent to be selected for a particular separation or extraction process. Therefore, the purpose of this study was to use KT (π^*) to predict the best co-solvent for $scCO_2$ to achieve the selective extraction of tocotrienols from PFAD. The work included a study of the extraction of PFAD using three polar co-solvents, ethanol, acetone, and isopropanol.

MATERIALS AND METHODS

Materials

PFAD was procured from Jomalina-Sime Darby (Teluk Panglima Garang, Selangor, Malaysia). For supercritical fluid extraction, liquid carbon dioxide at 99.99% (food grade) purity was purchased from Alpha Gas Solution Sdn. Bhd. (Shah Alam, Malaysia). All solvents used were either analytical grade or high-performance liquid chromatography (HPLC) grade, and were purchased from Sigma Aldrich (Kappelweg, Schnelldorf, Germany).

Dissolution of PFAD in Co-solvents

The solubility of PFAD in the co-solvents was tested using the same method as Lee *et al.* (2019). Preliminary experiments were carried out visually to identify the best co-solvents for the $scCO_2$ extraction and the ability of PFAD to dissolve in the mixed co-solvent. In a test tube, about 0.2 g PFAD was added to 4 mL of various solvents (ethanol, isopropanol, or acetone), and the mixture was heated to varying temperatures (40°C to 60°C) in a water bath, with continuous stirring for 5 min. The dissolution of PFAD was evaluated visually. This led to the identification of ethanol, isopropanol, and acetone as potentially good co-solvents for extracting tocotrienols from PFAD as tabulated in *Table 1*.

Supercritical Carbon Dioxide ($scCO_2$) Extraction Process

The extraction of tocotrienols from PFAD was conducted using laboratory-scale $scCO_2$ extraction with a 1 L extractor (dimension in meters: 0.21H x 0.08D) equipped with a CO_2 recirculating system. A fixed 100 g of pre-treated PFAD was weighed and loaded into the extractor vessel packed with glass beads and glass wool. Several methods have been suggested for the introduction of the co-solvent to the $scCO_2$ system, such as (1) directly adding the co-solvent to the sample, (2) pre-mixing the $scCO_2$ and co-solvent, and (3) using a secondary pump to add the co-solvent to the system (Putra *et al.*, 2018). Herein, PFAD was manually mixed with different amounts of the co-solvent (0.050, 0.075, 0.100 and 0.150 mL/g).

Dynamic extractions were continuously carried out for 6 hr at a flow rate of 32 ± 5 g/min, and extracts were collected at the separator in amber glass. Any residual co-solvent in the extracts was removed using a rotary evaporator (IKA RV 10 and IKA HB

10 control, Staufen, Germany) before the collected samples were stored at -20°C for further analysis.

Quantification of Tocotrienols

High-performance liquid chromatography (HPLC) was performed using an Agilent Technologies 1200 Series instrument with a diode-array detector (Agilent Technologies, United States) to identify and quantify the tocotrienol content of the PFAD extracts. As a standard for the tocotrienol quantification, a commercial tocotrienol product, Gold Tri. E 50 (99% pure), procured from Sime Darby, Malaysia, was used. A Kinetex PFP column with 150 x 4.6 mm i.d. and 5 µm particle diameter (Phenomenex, United States) was used for analysis. The injection volume was set at 6 µL, and the tocotrienol isomers were detected at the maximum absorption wavelength, 290 nm. The tocotrienol isomers separated from the extract at a flow rate of 0.6 mL/min with 85% (v/v) methanol in water for 50 min.

A Predictive Model of Kamlet-Taft (KT) Dipolarity/Polarisability

Duereh *et al*. (2019) developed a predictive framework to estimate the Kamlet-Taft (KT) dipolarity/polarisability parameter of the binary liquid mixture, $\Delta\pi^{*,N}_{mix}$. This model was proposed based on the linear relationship between the relative normalised dipolarity/ polarisability $\Delta\pi^{*,N}_{mix}$ of binary liquid polar-nonpolar mixtures which have a linear relationship and gas phase dipole moments. The predictive framework is used with the function of the Wilson thermodynamic excess function without considering the density dependency since the π* values of binary liquid mixtures do not significantly change with the density.

A modification to the predictive framework has been made by Duereh *et al*. (2020b) to predict the π* values of $scCO_2$-cosolvent binary mixtures. In this modification, density-dependent via a correction function ($g(\rho_{co_2})$) is added to the predictive framework. This is because a remarkable deviation between the experimental and predicted π* values using the previous predictive framework (Duereh *et al*., 2019) of $scCO_2$-cosolvent at 50°C and 10 MPa (supercritical region) were found. This suggested that density is another significant factor affecting the π* values at the supercritical phase instead of the dipole moment. The modification of the predictive framework as shown in Equation (1):

$$\Delta\pi^{*,N}_{mix} = \mu_2 \, [-x_1 \ln (x_1 + 1.981x_2) - x_2 \ln (x_2 + 0.181x_1)] \; x \; g(\rho_{co_2}) \tag{1}$$

where $\Delta\pi^{*,N}_{mix}$ is KT dipolarity/polarisability parameter of the $scCO_2$-cosolvent, μ_2 is dipole moment of cosolvent, x_1 is a composition of CO_2, x_2 is a composition of cosolvent, and $g(\rho_{co_2})$ is local density enhancement.

Four correction functions of local density enhancement have been evaluated by Duereh, *et al.* (2020b) using the fluorescence method, UV method, Raman method, and molecular dynamics simulations. Based on the plot of correction functions of local density enhancement as a function of pure density (ρ_{co_2}), which was estimated using Span and Wagner equation, the UV method was chosen since it sowed the smallest value of local density enhancement and almost symmetric shape compared to the other methods. The correction function using UV ($g^{UV}(\rho_{co_2})$) is as defined in Equation (2):

$$g^{UV} (\rho_{co_2}) = 1 + \{[0.937 \; X \; (1 - \exp (-3.916(\rho_{co_2}))] - 0.884 \, \rho_{co_2}\} \tag{2}$$

The predictive framework with the modification of local density enhancement using the UV method is shown in Equation (3):

$$\Delta\pi^{*,N}_{mix} = \mu_2 \, [-x_1 \ln (x_1 + 1.981x_2) - x_2 \ln (x_2 + 0.181x_1)] \; x \; \{1 + \{[0.937 \; X \; (1 - \exp (-3.916 \, \rho_{co_2}))] - 0.884 \, \rho_{co_2} \}\} \tag{3}$$

RESULTS AND DISCUSSION

Dissolution of PFAD in Various Co-solvents

To extend the $scCO_2$ solvating power and improve the affinity for polar compounds, adding small volumes of a (polar) co-solvent with the appropriate chemical and physical properties is necessary. The KT parameters dipolarity/ polarisability (π*), hydrogen-bond basicity (β), and hydrogen-bond acidity (α) effectively characterise potential solvents. Herein, three types of co-solvents (ethanol, isopropanol, and acetone) were chosen. The co-solvents were selected based on gas phase dipole moment and the function of the co-solvent as hydrogen bond donor or hydrogen bond acceptor. This is necessary to investigate the influence of dipole moment on the Kamlet-Taft dipolarity/ polarisability and the available specific interactions that can be formed between co-solvent and solute.

Table 1 explains that full PFAD dissolution was achieved with solvents that have α, β, and π* values in the range 0.08 to 0.86, 0.43 to 0.84 and 0.48 to 0.71, respectively. The dissolution tests of PFAD in ethanol, acetone and isopropanol at different temperatures are also shown in *Table 1*, with 4 mL of solvent mixed with 0.2 g PFAD for 5 min of stirring. It was found that PFAD was highly soluble in all three solvents at 40°C to 60°C. Increasing the temperature caused the viscosity of solvents to decrease, which gave high dissolution rates of the PFAD (Lee *et al.*, 2019). Since PFAD was highly soluble in the three solvents tested, they were all used as co-solvents in the $scCO_2$ extraction.

TABLE 1. KAMLET-TAFT PARAMETERS AND DISSOLUTION OF PFAD IN DIFFERENT CO-SOLVENTS

Solvent	Kamlet-Taft parameters			Solubility characteristics
	α	β	π*	
Acetone	0.08	0.43	0.71	Full dissolution at 40°C, 50°C and 60°C
Ethanol	0.86	0.75	0.54	Full dissolution at 40°C, 50°C and 60°C
Isopropanol	0.76	0.84	0.48	Full dissolution at 40°C, 50°C and 60°C

Note: α - hydrogen bond donor; β - hydrogen bond acceptor; π* - dipolarity; Kamlet-Taft parameters adapted from Weerachanchai *et al.* (2014).

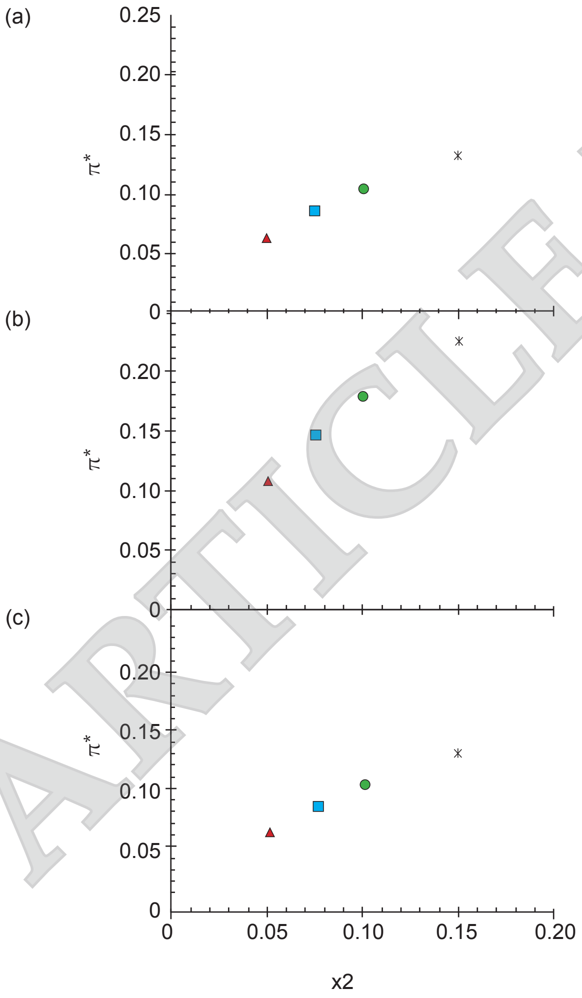

Figure 1. Kamlet-Taft dipolarity/polarisability (π) at 50°C and 20 MPa for (a) CO_2 (1)- C_2H_5OH (2), (b) CO_2 (1)- C_3H_6O (2), (c) CO_2 (1)- C_3H_8O (2) as a function of the amount of component 2. Symbol lists:* ▲ *= 0.05 mL/g,* ■ *= 0.075 mL/g,* ● *= 0.1 mL/g, and* ✳ *= 0.15 mL/g.*

KT Dipolarity/Polarisability of CO_2 and Co-solvent Mixtures

Figure 1 shows the $\Delta\pi^{*,N}_{mix}$ values for the binary mixtures of $scCO_2$ and various co-solvent (ethanol, acetone, and isopropanol) as estimated using the predictive model of KT dipolarity/polarisability to describe the co-solvent effects. Herein, the focus is only on the co-solvent composition and dipole moment towards the $\Delta\pi^{*,N}_{mix}$ values of the binary $scCO_2$-co-solvent system. π* increases as the co-solvent added in the $scCO_2$ system increases. Acetone (C_3H_6O) has higher π* values relatively compared to ethanol (C_2H_5OH) and isopropanol (C_3H_8O). This is because acetone has a higher dipole moment (2.88). The dipole moment governs the specific dipolarity/polarisability interactions between target compounds and the co-solvent in the supercritical state (Duereh *et al.*, 2020b). The molecular dynamics simulations showed the specific interactions that appeared between solute and co-solvent (Frolov and Kiselev, 2014; Gurina *et al.*, 2017). Hence, improve the solubility of target compounds in $scCO_2$ via the interactions. This has been proven by the infrared spectroscopic analyses (Lalanne *et al.*, 2004; Reilly *et al.*, 1995) and theoretical investigations (Danten, 2002; Saharay and Balasubramanian, 2006) whereby CO_2 can form the electron donor-acceptor interactions with the oxygen atom in alcohol co-solvent since CO_2 can act as a weak Lewis acid via electron deficiency in the carbon atom. Consequently, the π* values plotted in *Figure 1* follow the trend in values of the dipole moment of the co-solvents (*Table 2*).

TABLE 2. THE DIPOLE MOMENTS OF THE CO-SOLVENTS

Solvents	Dipole moment, μ
Ethanol	1.69
Acetone	2.88
Isopropanol	1.66

(Adapted from Duereh *et al.*, 2020a; 2020b).

In addition, the polarity can be estimated via π* to quantify the effect of co-solvent in the separation of the target compound in the sample. *Figure 2* depicts the relationship between the amount of tocotrienol extracted from PFAD and the estimated π* values of the solvent mixtures. The amount of tocotrienol extracted tended to increase linearly up to the particular value of π* but then started to decline as the estimated value of π* increased further for all mixtures of CO_2- C_2H_5OH, CO_2- C_3H_6O, and CO_2- C_3H_8O. Technically, during the extraction process, it is restricted by the equilibrium solubility of the solute in the solvent. Thus, the outer layer of solute is completely extracted by solvent. However, the extraction rate starts to decrease because many solutes have been extracted at the equilibrium

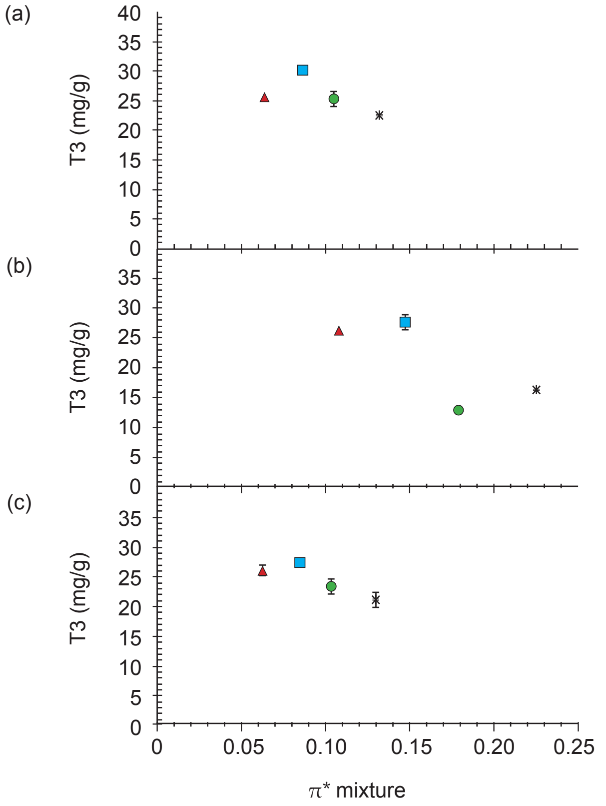

Figure 2. Tocotrienols extraction (mg/g) from PFAD as a function of Kamlet-Taft dipolarity/polarisability (π) of the mixtures of $scCO_2$ and (a) C_2H_5OH, (b) C_3H_6O and (c) C_3H_8O. Symbol lists: ▲ = 0.05 mL/g, ■ = 0.075 mL/g, ● = 0.1 mL/g, and ✱ = 0.15 mL/g.*

control phase. It can be noted that the extraction rate is reduced as the mass transfer decreases due to the free solute in the sample being depleted.

A more remarkable yield recovery is expected with the addition of co-solvent due to the polarity of tocotrienols. Instead of having only non-specific interaction via dispersion between CO_2 and solutes, the presence of co-solvent will create a more specific interaction via hydrogen bonding with the solute of interest, hence, improving the polarity. In the final stage of the extraction process, the diffusion control phase will take place, whereby the extraction of solute depends on the diffusion rate and ability of the solvent to penetrate deep into the sample to extract the remaining solutes. The addition of a co-solvent increases the density of the fluid mixture ($scCO_2$-cosolvent) around the solute, which causes the solid particles to swell, helping to break the chemical bonds and releases the soluble compounds, thus, enhancing the internal diffusion and solubilisation of interest compounds (Coelho *et al.*, 2020; Monroy *et al.*, 2016).

However, Machado *et al.* (2015) reported that a large amount of co-solvent will produce insufficient energy to break the bonds between the solvent molecules, and consequently, the solubility of polar compounds decreases. Besides, the saturation occurs between CO_2 and co-solvent when a higher amount of co-solvent is added to the system, leading to several phases such as liquid and gas phases will appear in the system (Yao *et al.*, 1994; Yoon *et al.*, 1994). It is important to note that the $scCO_2$ system should be maintained as a single homogenous phase. Other than that, a higher amount of co-solvent in the system will contribute to the solvent-solvent interactions in competition for the solvation of solutes, thus decreasing the recovery (Porto *et al.*, 2014). According to molecular dynamics simulations (Skarmoutsos *et al.*, 2010) and spectroscopic NMR (Maiwald *et al.*, 2007; Schnabel *et al.*, 2007), there is a possible self-hydrogen bonding interaction of alcohol co-solvents that appeared in a $scCO_2$-cosolvent system rather than forming the electron donor-acceptor interactions between CO_2 and alcohol co-solvents.

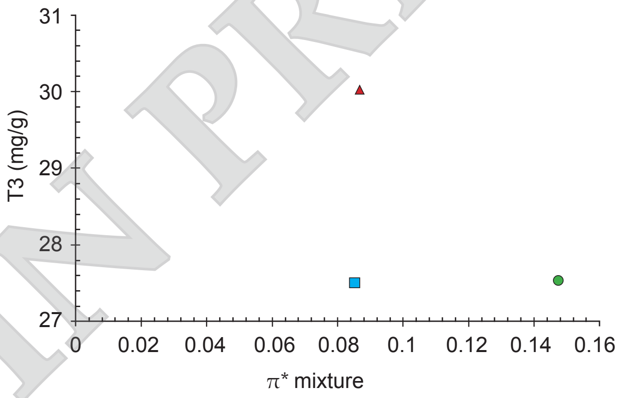

Figure 3. Recovery of tocotrienols from PFAD using $scCO_2$ with three different co-solvents (0.075 mL/g) at 50°C and 20 MPa as a function of Kamlet-Taft dipolarity/polarisability (π) of the CO_2- co-solvent mixtures in the supercritical state. Symbol list: ▲ = CO_2-C_2H_5OH, ■ = CO_2- C_3H_8O, and ● = CO_2-C_3H_6O.*

Figure 3 shows the recovery of tocotrienols from PFAD using $scCO_2$ with the addition of the different co-solvents. There is no significance different (*p*-value <0.05) between tocotrienols concentration among the three co-solvents, as depicted in *Table 3*. The most significant amount of tocotrienols extracted was 30.03 mg/g, with ethanol as the co-solvent in the $scCO_2$ system; the estimated value of π* for that mixture was 0.086. In principle, the dipole moment is an important factor influencing the π* value. As mentioned before, acetone had the highest π* value due to a large number of dipole moments. The change in π* values will create a specific interaction via hydrogen bonding between co-solvent and solute. However, the type of co-solvent is also another important factor. For instance, only one molecule in acetone will be involved in forming hydrogen bonding compared to ethanol. Thus, this is the limiting factor in the solubility of tocotrienols in the $scCO_2$-acetone system.

Ethanol can be considered a polarity-modifying solvent in $scCO_2$ extraction (Díaz-Reinoso *et al.*, 2020). As reported by Duereh and Smith (2018), the presence of ethanol at the supercritical state can increase both KT-polarisability and KT-basicity. Theoretically, CO_2 has low KT-basicity and dipolarity/polarisability. The KT-parameter can be changed over a narrow range of values (0-0.2) in the supercritical region. The addition of co-solvent such as ethanol may increase both KT-polarisability and KT-basicity, inducing the formation of both interactions (dispersion and hydrogen bonding), which enhance the solubility of the solute. More significant amounts of tocotrienols are extracted in the presence of ethanol because of the increase in the polarity of the solvent. Since tocotrienols contain hydroxyl groups (Coelho *et al.*, 2020), adding ethanol allows H-bonding between the co-solvent and the solute molecule, which increases the solubility of the compounds of interest in the $scCO_2$ phase (Coelho *et al.*, 2020). Furthermore, adding ethanol leads to swelling of the solid matrix, which facilitates the transport of the solute and so reduces the extraction time (Trevisani Juchen *et al.*, 2019). Several studies have evaluated $scCO_2$ with the addition of a co-solvent (Porto *et al.*, 2014; Sato *et al.*, 2017; Sookwong *et al.*, 2016).

Comparative Study of $scCO_2$, $scCO_2$ + Co-solvents, and Soxhlet Extraction

Three extraction techniques were compared, with Soxhlet extraction as a benchmark against evaluating the $scCO_2$ process. The extraction of tocotrienol using $scCO_2$ was significantly (p-value < 0.05) higher than that achieved by Soxhlet extraction (*Table 3*). This is due to the thermo-sensitivity of tocotrienols becoming important at the higher operating temperature of Soxhlet extraction (Ribeiro *et al.*, 2019). According to Othman *et al.* (2022), the tocotrienol extract increases when the temperature rises from 40°C to 50°C. However, a further increase in temperature may result in a reduction in tocotrienol extracts. Similarly, Zhao and Zhang (2014) found that the amount of 1,8-cineole extracted from Eucalyptus leaf oil was less with Soxhlet extraction than with $scCO_2$ extraction, and Jafarian *et al.* (2020) found that the extraction of phytosterols and tocopherols from rapeseed oil waste was greater with $scCO_2$ than with Soxhlet extraction.

$scCO_2$ has been categorised as a poor solvent for high molecular weight or hydrophilic compounds due to zero dipole moment (Zhang *et al.*, 2002). Significant changes of CO_2 π^* over a narrow range of value in the supercritical region leads to the interaction between CO_2 and many solutes through dispersion forces (Duereh and Smith, 2018). Nevertheless, the polarity of CO_2 can be switched since it is Lewis acid. Adding co-solvents to the $scCO_2$ increases the recovery of tocotrienols because the co-solvents polarity increases the dissolution of tocotrienols in PFAD. Tocotrienol extraction was approximately doubled with the addition of ethanol to the $scCO_2$ system compared with pure $scCO_2$, due to both specific (hydrogen bonding) and non-specific (dispersion) interactions between the co-solvent and the solute molecule, which increase the solubility of the tocotrienols in the solvent phase. According to and Waśkiewicz (2020), ethanol is generally employed in supercritical mixtures to improve the dissolvability of polar molecules and the selectivity of $scCO_2$. However, the main limitation of introducing co-solvent in the supercritical state is the phase equilibrium since it can reach saturation with excessive co-solvent presence in the $scCO_2$ system.

CONCLUSION

In this work, a predictive framework based on the values of CO_2 density, co-solvent dipole moment, and π^* of the pure components is proposed that allows estimation of the value of π^* for binary mixtures of $scCO_2$ and co-solvent (here, under the operating conditions of 20 MPa and 53°C). The estimates of π^* increase as the co-solvent in the binary mixture increases. Moreover, the extraction yield of tocotrienols was directly proportional to the π^* values of the binary mixtures as estimated using the predictive framework, but only up to a particular value of π^* after which it decreased as π^* increased

TABLE 3. EFFECT OF EXTRACTION CONDITIONS ON TOCOTRIENOLS CONCENTRATIONS (mg/g) IN PFAD EXTRACTS

Extraction condition		Tocotrienols (mg/g)
$scCO_2$		$16.45^b \pm 2.02$
$scCO_2$ + co-solvent	Ethanol	$30.03^a \pm 0.03$
	Acetone	$27.55^a \pm 1.44$
	Isopropanol	$27.51^a \pm 0.01$
Soxhlet extraction		$10.45^c \pm 0.57$

Note: Means that do not share superscript letters are significantly different (p-value < 0.05).

further. According to the predictive framework, ethanol is the best co-solvent for extracting tocotrienols from PFAD. This is due to the capability of ethanol to form more specific interactions with tocotrienols, which enhances the dissolution of tocotrienols in the $scCO_2$. The presence of ethanol as a co-solvent nearly doubled the extraction of tocotrienols (to 30.03 ± 0.03 mg/g) compared with that achieved by pure $scCO_2$ (16.45 ± 2.02 mg/g), and ethanol was slightly better in this respect than the other two co-solvents tested. This suggests that ethanol has excellent potential to be used to enhance the $scCO_2$ extraction of tocotrienols from PFAD.

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