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RESEARCH ARTICLE

Removal of Tetracycline Antibiotic Using Green Synergistic Extractive Extraction from Aqueous Solution

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Abstract Tetracycline antibiotic (TCA) is a broad-spectrum antibiotic that is extensively utilized in agriculture and human therapy. However, its extensive use poses significant environmental risks. Extractive extraction stands out as one of the effective methods available for TCA removal from aqueous solutions. The use of a single extractant in extractive extraction requires a high extractant concentration due to its low loading capacity. Therefore, this study aims to formulate a synergistic extractant diluted in green diluent (i.e., cooking palm oil). The synergistic extractant provides a high loading capacity and leads to improved extraction performance. The batch equilibrium experiment was performed to evaluate the extraction and stripping performance, where UV-Vis spectroscopy analysis was used to measure the change in TCA concentration in the aqueous solution before and after phase separation. The results show that nearly 98% of TCA (100 mg/L) can be extracted from the aqueous solution with 0.4 M bis-2-ethylhexyl phosphoric acid (D2EHPA)/0.0004 M tributyl phosphate (TBP). This combination achieves the highest synergistic coefficient value of 20.40, indicating a strong synergistic effect between the mixture of extractants. Additionally, about 98% of TCA can be stripped using 0.03 M hydrochloric acid (HCl). Hence, the formulated synergistic extractant, consisting of a mixture of D2EHPA and TBP, demonstrates significant potential for TCA removal from pharmaceutical wastewater.

Keywords: Tetracycline antibiotic, pharmaceutical wastewater, extractive extraction, synergistic formulation, green diluent.

Introduction

Antibiotics are one of the most regularly used medications and they are classified as a group of highly emerging and persistent group of pollutants that pose a high environmental risk [1]. The concentration of antibiotics detected in hospital and pharmaceutical industry wastewater ranges from 100 to 500 mg/L, which significantly exceeds the biodegradation capacity of ecosystems [2]. Tetracycline antibiotic (TCA) is categorized as a broad-spectrum antibiotic, mainly because of its extensive use in agriculture and human therapy which drives their high demand [3]. As such, TCA can enter water sources through various pathways and contaminate water streams. The accumulation of TCA can foster the development and propagation of antibiotic resistance, endangering the quality of drinking and irrigation water [4]. This situation presents a significant long-term threat to flora and fauna. Additionally, the amphoteric nature of TCA enables it to behave as an acid and base depending on the pH of its environment. In an environment with a pH less than 3.3, it can exist as a cationic species, between 3.3 and 7.7 as a zwitterionic, and a pH more than 7.7 as anionic species [5]. Given that the pH of pharmaceutical wastewater typically ranges from 1.0 to 8.0 [6,7], effective treatment is imperative to ensure the successful removal of TCA from pharmaceutical wastewater.

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Extractive extraction is widely utilized in various industrial applications due to its efficiency in separating and extracting a wide range of compounds and elements from complex mixtures [8]. Therefore, this method was applied for the removal of TCA from aqueous solutions. In this process, a specific amount of extractant (dissolved in a diluent) is necessary to extract the targeted solute through complexation in the organic phase until equilibrium is achieved [9]. However, employing a single extractant in the extractive extraction has certain disadvantages, notably the need for a high concentration of extractant due to the low solute loading capacity in the organic phase [10,11]. To overcome this limitation, a synergistic extractant is introduced.

A synergistic extractant refers to a mixture of two or more extractants to improve extraction performance beyond their single capabilities [12]. This process involves combining different types of extractants whose complementary mechanisms work together to produce a more efficient and selective extraction process [13]. The effectiveness of synergy in extractive extraction is indicated when the synergistic coefficient (SC) exceeds one. Conversely, an SC of less than one signifies an antagonistic effect, while an SC of one indicates no synergistic effect [14]. Utilizing a synergistic extractant from readily available single extractants is beneficial compared to the laborious process of developing new extractants. Several studies have successfully utilized synergistic extractive extraction for amoxicillin [15], phenol [16], gallium [17], and other compounds.

Towards a greener extraction process, researchers are moving forward to substitute petroleum-based diluents widely used in extractive extraction. The use of vegetable oils as a green diluent has become prominent within the last decade [18]. This growing interest is driven by the increasing focus on green chemistry, which aims to reduce or eliminate hazardous substances in chemical processes. This shift thereby promotes the transition from petroleum-based solvents to more environmentally benign alternatives such as vegetable oils.Vegetable oils are biodegradable and have lower toxicity [19]. Several studies have reported that using vegetable oils in extractive extraction also provides high extraction performance such as for platinum [8], lactic acid [20], butyric acid [21], synthetic dye [22], and others. This intensification of the extractive process aligns with the United Nations Sustainable Development Goals.

The combination of green diluent with synergistic extractant has not yet been explored. Thus, this study addresses this gap by introducing a novel and sustainable approach for efficient TCA removal. As far as we are aware, no studies have yet explored the application of a synergistic extractant embedded in a green diluent for TCA removal. The novelty of this green synergistic extraction process lies in leveraging green diluent, combining it with a mixture of extractants to enhance TCA removal efficiency, while ensuring sustainability and environmental safety. Therefore, this research aims to explore the potential of utilizing a synergistic extractant and a green diluent (specifically cooking palm oil) in the extractive extraction process to remove TCA from aqueous solution.

Materials and Methods

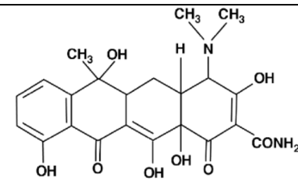
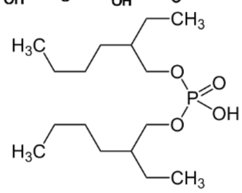
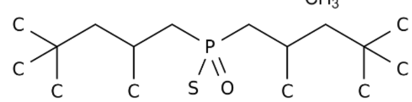
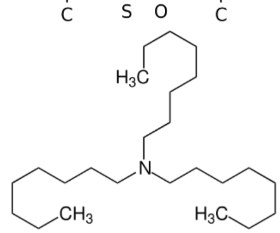
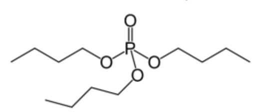
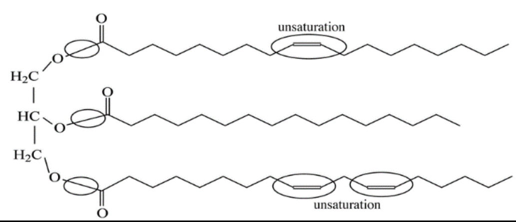
Materials

The simulated TCA solution (feed) was prepared by utilizing tetracycline hydrochloride (TCA·HCl, ≥98 % of purity) procured from Sigma-Aldrich. Several of the extractants used were di-2,4,4,-trimethylpentyl monothiophosphinic acid (Cyanex 302, Sigma-Aldrich, 85% of purity), bis-2-ethylhexyl phosphoric acid (D2EHPA, Merck, ≥95% of purity), trioctylamine (TOA, Sigma-Aldrich, 99% of purity), and tributyl phosphate (TBP, Sigma-Aldrich, 99% of purity). The cooking palm oil (Buruh) purchased from a local market was used as a green diluent. The stripping agent used was hydrochloric acid (HCl, Merck, 37% of purity). The chemical structure of TCA, extractants, cooking palm oil, and HCl are depicted in Table 1. All the chemicals and reagents specified are of analytical grade, requiring no further purification. In this study, the equipment utilized a Hanna Instruments pH Meter (HI-9813-51) for measuring the pH of the TCA solution, a Sastec incubator shaker for conducting green synergistic extractive extraction experiments, and a Spectrum lab 750 PRO UV-Vis Spectrophotometer for analyzing TCA concentrations.

Synergistic Extractant Formulation

The research aims to determine the most effective combination of the base and synergist extractants for the TCA extraction from the simulated TCA solution (feed phase) at a pH of 4.0. The extraction process was performed by mixing feed and organic phases (extractant in cooking palm oil) with an equivalent volume (10 ml) in a conical flask. Then, the solution was agitated in an incubator shaker at 300 rpm at 26°C for 18 hours to achieve equilibrium. Afterwards, the solution was poured and left in a separating funnel for 30 minutes to ensure complete phase separation. The concentration of TCA in the aqueous phase solution after the extraction process was analyzed via the UV-Vis spectrophotometer set to a wavelength of 360 nm [27]. The extractant that exhibited extraction performance at the highest was selected as the base extractant and mixed with the remaining extractants to develop the synergistic formulation. Equivalent volumes (10 mL) of the base and synergistic extractant were mixed, resulting in a total concentration of 0.1 M. The concentrations of extractant used in this study were determined based on preliminary experiments. Similarly, the extraction and separation processes, as well as TCA analysis, were conducted using the aforementioned methods. Fourier transform infrared (FTIR) spectroscopy was performed for the analysis of the complex formation in the organic phase containing TCA with extractant before and after extraction. Moreover, the slope analysis method was used to study the extraction mechanism [26].

Table 1. Chemical structure of TCA, extractants, cooking palm oil and HCl

Chemical	Structure	Reference
TCA		[4]
D2EHPA		[15]
Cyanex 302		[23]
TOA		[24]
TBP		[25]
Cooking palm oil		[26]

Stripping Agent Formulation

In this study, HCl was used as the potential stripping agent to strip TCA from the organic phase [27]. After achieving the best base and synergist extractant combination for higher TCA extraction, the stripping of TCA from the organic-loaded phase was performed. This involved mixing the TCA-loaded organic phase and HCl in the stripping phase with an equivalent volume (10 ml). The solution was agitated in an incubator shaker at 300 rpm at 26°C for 18 hours to achieve equilibrium. Subsequently, the solution was poured and left in a separating funnel for 30 minutes to ensure complete phase separation. In this study, the concentrations of stripping agents used were determined based on preliminary experiments. The same procedure was then used to analyze TCA concentration in the stripping phase. The stripping mechanism for TCA was also determined using the slope of analysis method [26].

Data Analysis

In this study, the extraction performance (E), distribution ratio (D), SC, and stripping performance (S) were calculated using Eqs. (1-4), respectively:

$$E\ (\%) = \frac{C_i - C_{aq}}{C_i} \times 100 \quad (1)$$

$$D = \frac{C_{org}}{C_{aq}} \quad (2)$$

$$SC = \frac{D_{mixture}}{D_{base} + D_{extractant}} \quad (3)$$

$$S\ (\%) = \frac{C_s}{C_{org}} \times 100 \quad (4)$$

where C_i is the TCA initial concentration (in mg/L) in the feed phase. C_{aq} and C_s are the TCA concentration (in mg/L) of the aqueous phase and stripping phase after the extraction and stripping process, respectively. Meanwhile, C_{org} denotes the TCA concentration (in mg/L) after the extraction process in the organic phase. $D_{mixture}$ is associated with the distribution ratio of the synergistic extraction process, while D_{base} and $D_{synergist}$ refer to the distribution ratios of a base and synergist extractant, respectively. The experimental data were reported as triplicates with a standard deviation of less than 1%.

Results and Discussion

Effect of Single Extractant

The effect of a single extractant for TCA extraction was investigated with results depicted in Figure 1. The results demonstrate that the extraction performance in this study decreased in the following sequence: D2EHPA (40.57%) > TBP (5.65%) > TOA (4.67%) > Cyanex 302 (3.87%) > no extractant (2.63%). From these results, it can be ascribed that the extraction mechanism of TCA is via complexation. This means that TCA can react with or without the presence of an extractant. In the absence of an extractant, TCA can react with the triglycerides present in cooking palm oil [28]. However, the extraction of TCA is low at 2.62% which is insignificant. Therefore, the addition of an extractant is necessary to facilitate and improve the extraction of TCA. Accordingly, extractants can improve the extraction performance by facilitating specific interactions and increasing the solute solubility in the organic phase [18].

For acidic extractants, D2EHPA (P=O) provided the highest extraction performance compared to Cyanex 302 (P=S). This can be attributed to D2EHPA demonstrating the highest acidity [29], which facilitates the substitution of the hydrogen atom in the P–O–H bond of D2EHPA with the TCA. The extraction mechanism relies on protonation and hydrogen bonding interactions, where the highest acidity of D2EHPA enhances its ability to form electrostatic interactions and ion-pair complexes with TCA more efficiently. The formation of these complexes is further confirmed through FTIR spectroscopy analysis, which will be discussed in detail later. Meanwhile, the use of TOA as a basic extractant demonstrated a low TCA extraction. This can be attributed to the fact that an amine-based extractant is more effective in extracting anionic complexes from basic solutions through an anion exchange mechanism [30]. Conversely, TBP, which acts as a neutral extractant also shows low extraction performance for TCA. This is attributed to its tendency to form various complexes with the green diluent (i.e., cooking palm oil), which is consistent with the results of Nurulashikin *et al*. [31]. Since D2EHPA achieved the highest extraction of TCA, it was chosen as the base extractant to be synergized with the remaining extractants.

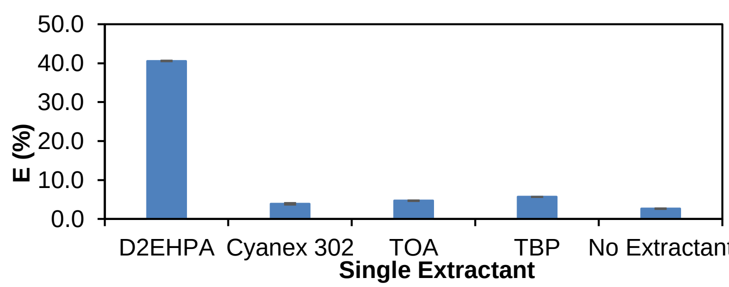


Figure 1. Effect of single extractant on TCA extraction (Experimental conditions: [TCA] = 100 mg/L), pH of TCA solution = 4.0, [extractant] = 0.1 M, diluent = cooking palm oil, aqueous:organic ratio = 1:1, temperature = 26 ºC, extraction time = 18 hr, agitation speed = 300 rpm)

Effect of Mixture Extractant

For the synergism between D2EHPA with other extractants, the synergist effect can be assessed through the determination of the SC value and the results are presented in Table 2. In this study, only the mixture of D2EHPA and TBP demonstrated a synergistic effect (SC = 1.05) with 18.19% of TCA extracted into the organic phase. This can be attributed to D2EHPA as an extractant being more pronounced than TBP in the extraction of TCA, indicating that TBP acts as a modifier [25] and does not participate in the complexation to extract TCA. Meanwhile, the inclusion of TBP in D2EHPA creates a synergistic effect in the extraction system by enhancing the solubility of the extraction complex in the organic phase [32].

Table 2. Effect of different types of mixture extractant (Experimental conditions: [TCA] = 100 mg/L), pH of TCA solution = 4.0, [mixture extractant] = 0.1 M, diluent = cooking palm oil, aqueous:organic ratio = 1:1, temperature = 26 ºC, extraction time = 18 hr, agitation speed = 300 rpm)

Synergist Extractant (0.05 M)	Base Extractant (0.05 M)	
	D2EHPA	
	E (%)	SC
Cyanex 302	9.79	0.66
TOA	0.89	0.04
TBP	18.19	1.05

On the other hand, other mixtures exhibited antagonistic effects (SC<1) with less than 10% TCA extraction. This phenomenon is due to structural changes in D2EHPA upon the addition of Cyanex 302 and TOA inhibiting the formation of a complex with TCA. This aligns with the study by Dashti *et al*. [33], who reported an antagonistic effect when using a Cyanex 572/Alamine 336 mixture to extract rare earth elements. Moreover, Jusoh *et al* [24] reported that a TOA/Cyanex 302 is the only mixture extractant that exhibited a synergistic effect for turquoise blue extraction, while mixtures of TOA with other extractants showed antagonistic effects due to the incompatibility between the extractants. Thus, in this study, the mixture of D2EHPA and TBP was selected as the best mixture extractant. Nevertheless, it is crucial to determine the best concentration of the extractant mixture to ensure the high extraction performance of TCA.

Effect of Mixture Extractant Concentration

The determination of a suitable concentration of each extractant is very important, as each one influences the extraction of TCA differently. The extraction performance of TCA utilizing the mixture extractant of D2EHPA and TBP. The results show that upon increasing the D2EHPA concentration (0.1-0.4 M) at a fixed TBP concentration, the extraction performance of TCA increased significantly up to 97.82%. The increase in D2EHPA concentration improves its effectiveness in extracting TCA. These results are also in accordance with Le Châtelier's principle, demonstrating that higher extractant concentration enhances solute extraction performance [25]. As depicted in Table 3, D2EHPA had a significant influence on the extraction of TCA.

Table 3. Effect of mixture extractant concentration (Experimental conditions: [TCA] = 100 mg/L), pH of TCA solution = 4.0, mixture extractant = D2EHPA + TBP, diluent = cooking palm oil, aqueous:organic ratio = 1:1, temperature = 26 ºC, extraction time = 18 hr, agitation speed = 300 rpm)

[D2EHPA] (M)	[TBP] (M)									
	0.0001		0.0002		0.0003		0.0004		0.0005	
	E (%)	SC	E (%)	SC	E (%)	SC	E (%)	SC	E (%)	SC
0.1	55.16	1.65	60.94	2.11	63.43	2.34	62.37	2.24	52.18	1.60
0.2	74.11	1.81	77.80	2.23	81.63	2.83	82.25	2.95	77.58	2.20
0.3	79.45	2.33	87.01	4.05	90.88	6.03	93.15	8.22	91.19	6.26
0.4	89.68	3.95	91.77	5.07	95.73	10.19	97.82	20.40	95.55	9.76

Meanwhile, increasing the TBP concentration (0.0001-0.0005 M) at a fixed D2EHPA concentration also increases the extraction performance of TCA. However, at a certain concentration of TBP, the extraction performance of TCA decreases. The excessive use of TBP negatively affected the extraction of TCA. At higher concentrations, TBP can interact with D2EHPA whereby in this case it functioned as a neutral extractant and formed a neutral complex [34]. This complex formation reduces the effectiveness of D2EHPA concentration in the solvent, thereby decreasing the TCA extraction performance. It can be deduced that the concentration of D2EHPA in the mixed extractant system influences the extraction of

TCA. Hence, the best extractant mixture achieving nearly 98% of TCA extraction with an SC value of 20.40 consists of 0.4 M D2EHPA/0.0004 M TBP.

Aside from that, the slope analysis method was used to determine the extraction mechanism in which the graph of Log D as a function of Log [D2EHPA] was constructed as shown in Figure 2. The slope of the graph represented the mole number of D2EHPA involved in the reaction for TCA extraction. From the graph, the slope is around 1.5, suggesting that two moles of TCA required three moles of D2EHPA during the extraction process. Eq. (5) signifies the reaction of D2EHPA and TCA at the aqueous/organic interface to form TCA complexes.

$$2TCA_{(aq)} + 3(RH)_{2(org)} \rightarrow 2[TCA \cdot R(RH)_2]_{(org)} + H_{2(g)} \quad (5)$$

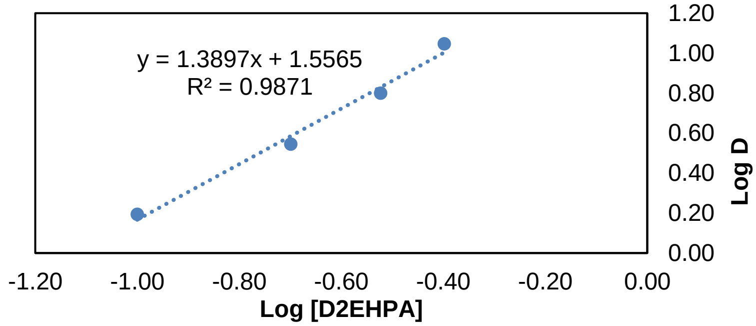


Figure 2. Stoichiometry for the equilibrium extraction of TCA using D2EHPA

FTIR Spectroscopy Analysis

In this study, the organic phase consists of a mixture of D2EHPA and TBP diluted in cooking palm oil for the removal of TCA from an aqueous solution. The FTIR spectra of D2EHPA/TBP before and after the extraction process are depicted in Figure 3. The C–H symmetrical and asymmetrical of the alkane groups existing in cooking palm oil correspond at the regions of 3006 cm^{-1}, 2922 cm^{-1} and 2853 cm^{-1} [35]. Meanwhile, the C=O stretching, C–O stretching and C=C bending of triglyceride in the cooking palm oil are attributed at peaks 1744 cm^{-1}, 1160 cm^{-1} and 722 cm^{-1}, respectively [36]. Moreover, the FTIR bands at 1461 cm^{-1} and 1377 cm^{-1} were associated with the bending vibration of the alkane group, whereas the band at 1116 cm^{-1} also corresponded to the stretching vibration of C=O of triglyceride in the same oil [35]. The spectra show vibration bands at region 1033 cm^{-1} and 1233 cm^{-1} for P–O–H and P=O, respectively for D2EHPA in the organic phase [37]. It is also observed that that there is no change in the characteristic vibration of the other bands such as P=O (1233 cm^{-1}). Aside from that, the weaker intensity of the P–O–H in D2EHPA/TBP after the extraction process suggests the complexation of D2EHPA with TCA in the organic phase.

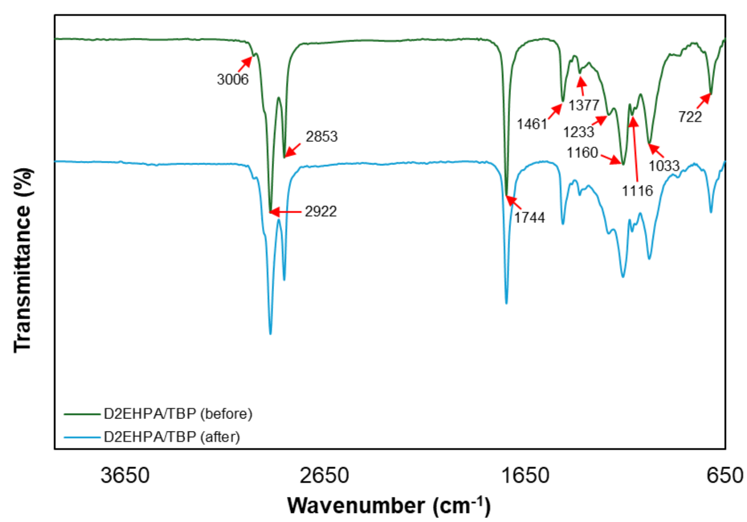


Figure 3. FTIR spectra of the organic phases with D2EHPA/TBP

Effect of Stripping Agent Concentration

The concentration of stripping agent (HCl) was investigated from 0.005 to 0.05 M to strip TCA (97.82 mg/L) from the organic phase as presented in Figure 4. The stripping performance of TCA increased from 39.34 to 98.32% when increasing HCl concentration from 0.005 to 0.03 M. The stripping agent with a high concentration results in a greater number of stripping agent molecules [32], thereby enhancing the extent of the decomplexation of the TCA-extractant. In contrast, the stripping performance of TCA was reduced to 32.15% when further increasing the HCl concentration to 0.05 M. At a high HCl concentration, the visibly cloudy solution was observed in the stripping phase. This cloudiness could be due to the interaction of chloride ions with various complex molecules, potentially leading to precipitation and thereby affecting the performance of the stripping process for TCA. A study suggests that increased chloride ions may interact with triglycerides to form a different compound, causing the aqueous solution to become cloudy [22]. Hence, the best concentration of stripping agent at 0.03 M of HCl was chosen to strip TCA from the organic phase.

The slope analysis method was also used for the stripping mechanism, the graph of Log D as a function of Log [HCl] was constructed as presented in Figure 5. The graph shows a straight line with a slope around 2.5, signifying that five moles of HCl are required for two moles of TCA-D2EHPA complexes during the stripping process. Eq. (6) represents the reaction of loaded TCA-D2EHPA complexes with HCl.

$$2[TCA \cdot R(RH)_2]_{(org)} + 5HCl_{(aq)} \rightarrow 2(TCA \cdot H^+Cl^-)_{(aq)} + H^+_{(aq)} + 3Cl^-{}_{(aq)} + 3(RH)_{2(org)} \quad (6)$$

Conclusions and Future Prospects

The synergistic extractant formulation for TCA extraction from aqueous solution was successfully investigated. This formulation features the synergism of D2EHPA and TBP, with D2EHPA acting as the base extractant and TBP as the synergistic extractant. A maximum extraction performance of almost 98% was achieved with 0.4 M D2EHPA/0.0004 M TBP. Meanwhile, 0.03 M HCl demonstrated the highest stripping performance at 98.32%. Thus, the implementation of the green synergistic extractive extraction approach resulted in improved performance and indicated a strong potential for the removal of TCA from pharmaceutical wastewater. In future studies, researchers should also emphasize investigating the influence of pH on the TCA removal performance from aqueous solutions to correspond with the pH of real pharmaceutical wastewater. In addition, to ensure the selective removal of very low concentrations of TCA in pharmaceutical wastewater and allow the safe discharge of treated wastewater into water bodies, various methods can be integrated such as adsorption [38], membrane technology [39], and advanced oxidation processes [40].

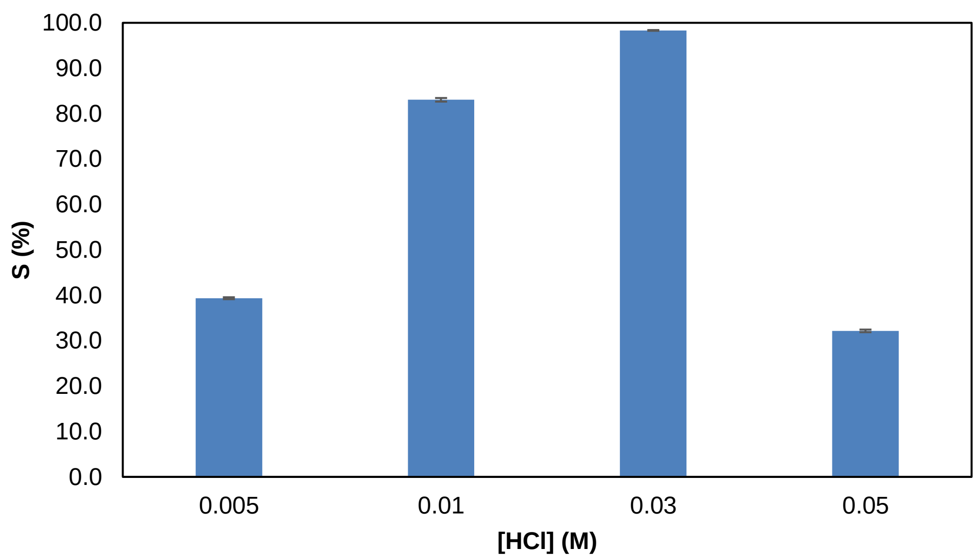


Figure 4. Effect of stripping agent concentration (Experimental conditions: [TCA] = 97.82 mg/L), [D2EHPA] = 0.4 M, [TBP] = 0.0004M, diluent = cooking palm oil, aqueous:organic ratio = 1:1, temperature = 26 ºC, stripping time = 18 hr, agitation speed = 300 rpm)

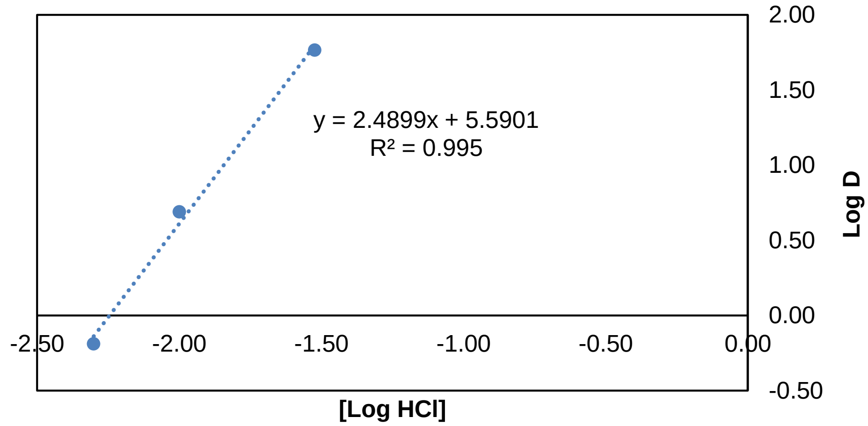


Figure 5. Stoichiometry for the equilibrium stripping of TCA using HCl

Conflicts of Interest

The author(s) affirm(s) that there are no conflicts of interest in connection with the publication of this research article.

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