An effective dispersive liquid-liquid microextraction method for pharmaceutical extraction: Optimization via central composite design

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Abstract

In this study, a simple and efficient dispersive liquid-liquid microextraction procedure (DLLME) was developed to remove diclofenac sodium (DF) from water samples. Various parameters such as diclofenac concentration in aqueous phase (10-50 mg/L), process time (2-10 min), extraction solvent concentration (0.005-0.025 M), and centrifuge speed (1000-5000 rpm) were investigated. The experimental design was performed by the Response Surface Methodology (RSM) according to the central composite design to reduce the number of experiments and determine the optimal extraction conditions. The effect of the single and simultaneous operational parameters was evaluated. In this regard, the extraction concentration of 0.01 M, the initial diclofenac concentration in aqueous phase 20 mg/L, the rotation speed of the centrifuge 4000 rpm, and the residence time of 8 min were obtained as the optimum operating conditions. According to the other studies and available findings, the ratio of two-phase organic and aqueous discharges (Q_{org}/Q_{aq}) was set to 1:9. The diclofenac extraction from the aqueous phase was 77.91% in optimum operating conditions.

Keywords: Dispersive Liquid-liquid microextraction; Solvent extraction; Diclofenac; Response Surface Methodology.

1. Introduction

Diclofenac sodium is a non-steroidal anti-inflammatory medicine that has been used in humans since the 1970s. By blocking the effect of the enzyme cyclooxygenase, this drug reduces the production of a prostaglandin chemical in the body, responsible for causing pain and inflammation in the affected area [1–5]. In present days, one of the most crucial environmental problems is the emerging contaminant from the pharmaceutical industry, hospitals, and home drains in aquatic environments because of their persistence and potentially harmful effects on any form of aquatic life. Diclofenac accumulates in edible fruits and vegetables, having a direct effect on human health. Additionally, several research on the toxicity of diclofenac on birds, mammals, aquatic species, and plants have been published [6–10].

The sample preparation phase is an extremely important part of the analysis process. In this step, a desired component will be extracted from purified and concentrated. There are a variety of preparation methods available, each with its own advantages in terms of speed and ease [11]. The selection of each technique is dependent on the analyte conditions, both physical and chemical [12–17]. Liquid-Liquid extraction has long been one of the most common methods of separating contaminants. The long process time, high solvent and extraction solvent consumption, the possibility of emulsion formation, and the need for intense mixing have made the use of this method difficult. To address the limitations of liquid-liquid extraction, liquid-phase microextraction methods (LPME) have been developed.

LPMEs may be classified into four broad categories: (a) single drop microextraction (SDME); (b) continuous flow microextraction (CFME); (c) hollow fiber liquid-phase microextraction (HF-LPME); and (d) dispersive liquid-liquid microextraction (DLLME). These are different in how the solvent contacts the aqueous phase [18–27].

In this research, a dispersive liquid-liquid microextraction method has been applied to separate the diclofenac from an aqueous solution. DLLME system consists of three components: water is a common part (aqueous sample), and about the other two components, one of them is insoluble in water (extraction solvent), and the other one is soluble in the other two components (dispersive solvent).

DLLME protocols are typically composed of the following steps: an extraction solvent is combined with a dispersive solvent, and the solvent mixture is then quickly injected into an aqueous sample. An aqueous sample is rapidly injected with an extraction-dispersive solvent mixture, resulting in the formation of a cloudy solution composed of microdroplets of extraction solvent scattered throughout the sample. Cloudy solution production allows for the immediate partitioning of analytes from the aqueous sample into the extraction phase, which is advantageous in some cases (a major advantage of this technique). Using centrifugation, the hazy solution is separated into two phases, allowing for the simple recovery of the extraction solvent for subsequent examination of the results [28]. This method, for its very simple texture, is well compatible with most instrumental methods. For example, in gas chromatography, liquid chromatography, Ultraviolet-visible spectrometry, and flame atomic absorption spectrometry, the organic solvent can be inducted directly into the analysis instrument [29,30].

2. Materials and methods

2.1. Material

Diclofenac sodium (Sodium 2-[2-[(2,6dichlorophenyl)amino]acetate, $C_{14}H_{10}C1_2NNaO_2$), a white powder with more than 98% purity, was supplied by Sigma-Aldrich (Steinheim, Germany)

(Table 1). n-Butanol as an organic solvent and Tetra-n-butylammonium bromide (TBAB) was provided by Merck Co.(Germany). TBAB is added to the solvent phase, and its cationic form is complexed with the anionic form of the diclofenac. In the dispersive liquid-liquid microextraction, the extraction solvent was selected from solvents that, in addition to being insoluble in water and having a higher density than water, could extract the desired compound [30,31]. Also, the base of the dispersive solvent is its solubility in both the aqueous phase of the sample and the organic phase of the extractor. Due to the physical and chemical properties, TBAB was selected as the dispersive solvent with the highest recycling rate.

2.2. Instrumental

The ultraviolet-visible (UV-vis spectrophotometry (Shimadzu UV-1800, Japan)) method was applied to measure and determine the concentration of diclofenac in the aqueous sample. Centrifuged (EBA 20-Hettich, Germany) was used to centrifuge the sample. In order to measure and control the pH during the experiments related to this research, a pH meter (PL-700PV model, Taiwan) was used.

2.3. Procedure

n-Butanol as an extraction solvent and TBAB as a dispersive solvent were considered. We experimented with the preconcentration of diclofenac according to the dispersive liquid-liquid microextraction method. The influential factors such as diclofenac concentration in aqueous phase (10-50 mg/L), process time (2-10 min), extraction solvent concentration (0.005-0.025 M), and centrifuge speed (1000-5000 rpm) were also considered for the focus of determining optimal values. During the process, diclofenac concentrations in the aqueous phase ranged from 10 to 50

112 mg/L with a constant 1:9 ratio of organic to aqueous phases including butanol and at 1000 to
113 5000 rpm were evaluated at various times. The calibration curve of diclofenac was prepared
114 based on 1, 5, 10, 15, 20, 30, and 40 mg/L concentrations. 5 mL of each sample was taken and
115 analyzed by spectrometry (Fig. 1(a)). In general, the maximum absorption of diclofenac occurs at
116 275 nm wavelength. By linear fitting of the points obtained from the visible-ultraviolet
117 spectrometry analysis, the calibration curve with the coefficient of determination close to 1 (R^2=
118 0.998) was obtained (Fig. 1(b)). Using this line equation, the concentration of diclofenac in
119 unknown samples can be calculated.
120
121 The extraction efficiency (EE (%)) was used for determining the mass transfer performance, and
122 the Eq. (1) can be used for the calculation of EE%.

$$EE(\%) = \frac{C_{aq,in} - C_{aq,out}}{C_{aq,in}} \times 100 \quad (1)$$

123 $C_{aq,in}$ $C_{aq,out}$ (mg/L) are input concentration and output concentration, respectively.
124 Response surface approach based on the central composite design was used to optimize the
125 independent factors that influenced the process efficiency in the evaluation of extraction
126 efficiency in the dispersive liquid-liquid microextraction method. Independent variables, namely
127 diclofenac concentration in aqueous phase (A), process time (B), extraction solvent
128 concentration (C), and centrifuge speed (D), were selected in five levels with three replicable
129 center points. The selected ranges and levels of each factor are shown in Table 2. Also, 27 tests
130 as per the central composite design (CCD) to evaluate the effect of variables and optimize them
131 for diclofenac extraction were performed, as shown in Table 3 [32,33].
132

3. Results and discussion

3.1. The pH effect

The effect of solution pH on the rate of diclofenac extraction from the aqueous phase by extractor with a concentration of 0.01 M, diclofenac concentration in 20 mg/L, the rotation speed of the centrifuge 3000 rpm, and the residence time of 6 min have been investigated as a single factor, which is shown in Fig. 2. As can be observed in Fig. 2, the pH of the diclofenac samples was adjusted by using NaOH or HNO_3 solutions. The extraction efficiency is reduced by decreasing the pH to less than 4. Given that the ionization constant of diclofenac is 4.16, diclofenac is protonated at a pH less than 4.16, resulting in an acidic form, which is reduced to form complexes with TBAB. As pH increased, the ionized form of diclofenac increased, which resulted in an increase in complex formation, so extraction efficiency increased. The decreases in extraction efficiency at alkaline pH can be attributable to OH and diclofenac ions competing with one another for bonds with extractant molecules [34]. In all experiments performed, the aqueous phase pH was set to 5 because the maximum extraction rate was obtained at pH 5.

3.2. **Statistical design**

After performing experiments with the surface response method, the concentration of the aqueous phase after each experiment was analyzed to calculate the extraction efficiency of diclofenac. As a function of factors independent of the process used for diclofenac extraction by liquid-liquid microextraction method, a quadratic polynomial model is derived as Eq. (2):

$$EE(\%) = +36.38 -11.94A +2.79B +2.10C +4.50D -7.53AC -10.65AD +2.18BD -11.31CD +1.96A^2 +0.0828B^2 +3.10C^2 \quad (2)$$

According to Eq. (2), E indicates the percentage of diclofenac extracted; A, B, C, and D also represent the diclofenac concentration in aqueous phase, process time, extraction solvent concentration, and centrifuge speed the extraction, respectively. Also, the laboratory values for diclofenac extraction efficiency obtained by Eq. (1) and predicted by Eq. (2) were summarized in Table 4. A maximum laboratory value (80.88) and predicted value (78.81) for diclofenac extraction efficiency can be found in run7, which includes diclofenac concentration in aqueous phase 20 mg/L, process time 8 minutes, extraction solvent concentration 0.02 M, centrifuge speed 4000 rpm.

An analysis of variance (ANOVA) was carried out to determine the impact of process variables on diclofenac extraction efficiency, and the results are listed in Table 5. The values of F and p for each factor are expressed. The analysis considers the 95% confidence interval, so each factor's p-value indicates the significance or insignificance of that factor in the model [35]. In accordance with the analysis of variance, the p-value for the selected model for diclofenac extraction is less than 0.05; it indicates that the chosen model is statistically significant. In contrast, the value of the model coefficient for the fitted model was 0.9751. The values of the adjusted coefficient of determination and the predicted coefficient of determination were 0.9461 and 0.8590, respectively, which shows that the selected model is able to cover laboratory data relatively well [36]. Also, based on Fig.3, there is a good correlation between the predicted and laboratory values of extraction efficiency, respectively.

3.3. Interaction of operational parameters on diclofenac extraction

In order to investigate the interaction of variables, contour plots and three-dimensional diagrams of the effect of parameters on the efficiency of diclofenac extraction by DLLME were drawn by changing the values of two parameters and maintaining the other parameter constant. As shown in Fig. 4(a), the extraction efficiency has increased with increasing time and decreasing the feed phase's initial concentration. In fact, initial increase in extraction time promotes the solute transfer, thereby increasing the extraction performance. Experiments by many previous researchers indicated that the emulsion breakage increases with increase in extraction time due to gradual increase of swelling [37–39]. In Fig. 4(b), as the concentration of the extraction solvent increases, the extraction efficiency of diclofenac increases more than the concentration of the aqueous phase. Also, the extraction efficiency has increased by increasing the extraction concentration and decreasing the feed phase's initial concentration. This can be due to the organic phase being saturated with a diclofenac complex. Initially, at low concentrations of the feed phase, the transfer of diclofenac depends on the activity of the extraction, but at high concentrations, the activity coefficient is due to the colombian interaction between anion and cation. Due to the increase in ionic strength, it leads to low salt activity and thus reduces extraction [40]. Fig. 4(c) shows that the effect of centrifuge rotation speed on diclofenac extraction efficiency is greater than the initial diclofenac concentration in aqueous phase. Also, the extraction efficiency has increased by increasing the centrifuge's rotation speed and decreasing the initial concentration of the feed phase. In fact, an increase in mixing speed would increase interfacial area and the mass transfer coefficient, thereby increasing overall enrichment and extraction [41]. Fig. 5(a) shows that the effects of both factors on diclofenac extraction efficiency are very close to each other. Also, with increase the extraction concentration and

increasing the extraction time, the extraction efficiency has increased. According to Fig. 5(b), the effect of both factors on diclofenac extraction efficiency is relatively similar. Also, the extraction efficiency has increased with increasing the centrifuge's rotation speed and increasing the extraction time. Finally, in Fig. 5(c), it is apparent that the extraction efficiency increases with increasing the extractor concentration and centrifuge rotation speed.

3.3. Determination of the values of the parameters in the optimum state

After investigating the effect of process variables on diclofenac extraction in the organic solvent, these variables' values can be obtained in the optimal state to achieve maximum efficiency. For this purpose, the optimization part of Design-Expert software was used. The diclofenac extraction process's optimal conditions were included 20 mg/L initial concentration of the aqueous phase, 0.01 M extraction concentration, the centrifuge rotation speed of 4000 rpm, and residence time of 8 min (Table 6). The extraction percentage of diclofenac is predicted to be 78.78% based on these values. Under optimal conditions, the extraction percentage was 77.91%, which indicates that the fitted model is accurate.

4. Conclusion

In this study, the DLLME method was successfully applied to the extraction of diclofenac from aqueous samples. The effect of parameters such as initial aqueous phase concentration, extractor concentration, centrifuge rotation speed, and residence time under test design and pH at the optimum point as a single factor was investigated. An analysis of variance was performed to determine whether operational parameters affected the rate of diclofenac extraction. A quadratic

mathematical model with a reliability coefficient of 0.975 was developed to predict the amount of diclofenac extraction from the aqueous phase by dispersive-liquid-liquid microextraction. Based on the results, 0.01 M extraction concentration, 20 mg/L initial aqueous phase concentration, 4000 rpm centrifugation speed, 8-minute residence time, and pH 5 were determined to be the optimal conditions for the extraction. Under these conditions, the extraction efficiency was 77.91%. Since diclofenac effluents create environmental issues, the micro-aqueous organic system may be a viable solution due to the smaller organic phase than aqueous extraction, as well as the quick extraction time.

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Figure captions

Fig. 1. (a) Visible spectrum – ultraviolet of diclofenac sodium at the various concentration (1-50 mg/L) and (b) diclofenac sodium calibration curve.

Fig. 2. The effect of feed phase pH on extraction efficiency.

Fig. 3. Correlation between predicted and laboratory values of extraction efficiency.

Fig. 4. The response levels simultaneously interaction between initial diclofenac concentration in aqueous phase (a) process time, (b) solvent concentration, and (c) centrifuge speed on the DF extraction.

Fig. 5. The response levels simultaneously interaction between (a) process time and solvent concentration, (b) process time and centrifuge speed, and (c) solvent concentration and centrifuge speed on the DF extraction.

Table captions

Table 1. Physical and chemical properties of diclofenac sodium.

Table 2. The selected ranges and levels in diclofenac extraction efficiency.

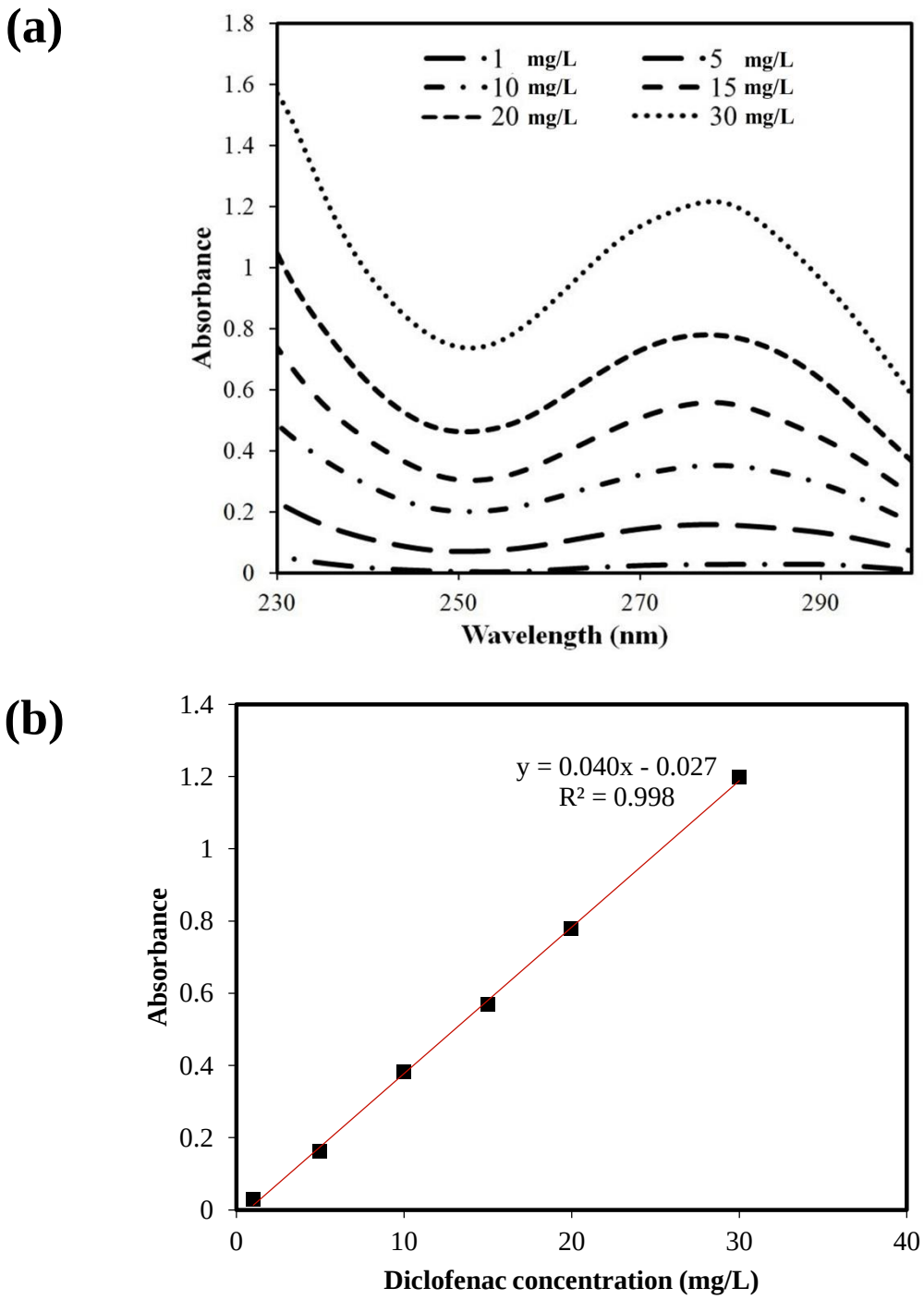
Table 3. Central composite design.

Table 4. Calculated and predicted results of diclofenac extraction efficiency.

Table 5. analysis of variance for diclofenac liquid-liquid microextraction.

Table 6. Optimal values of parameters and percentage of predicted and experimental extraction.

Fig. 1. (a) Visible spectrum – ultraviolet of diclofenac sodium at the various concentration (1-50 mg/L) and (b) diclofenac sodium calibration curve.



423 Fig. 2. The effect of feed phase pH on extraction efficiency.

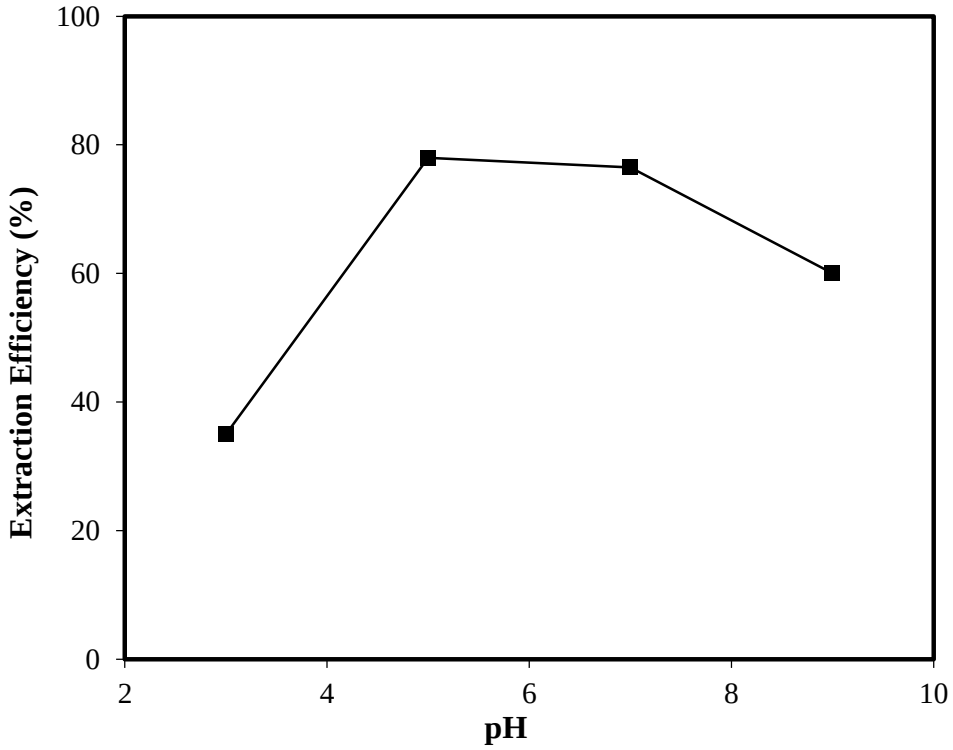


Fig. 3. Correlation between predicted and laboratory values of extraction efficiency.

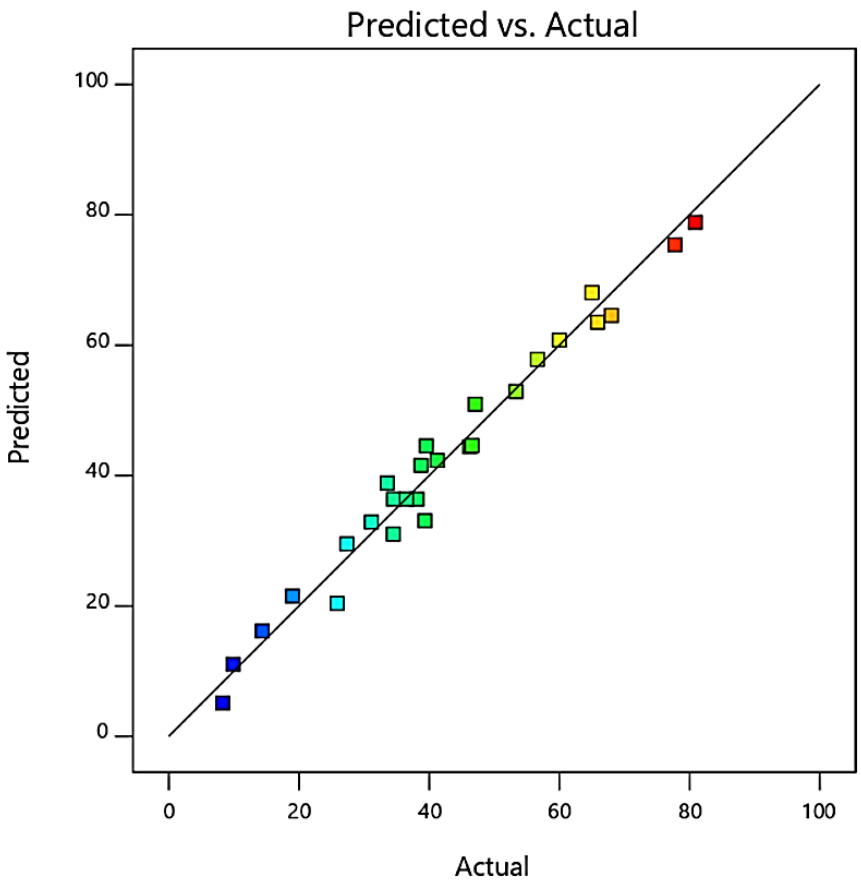
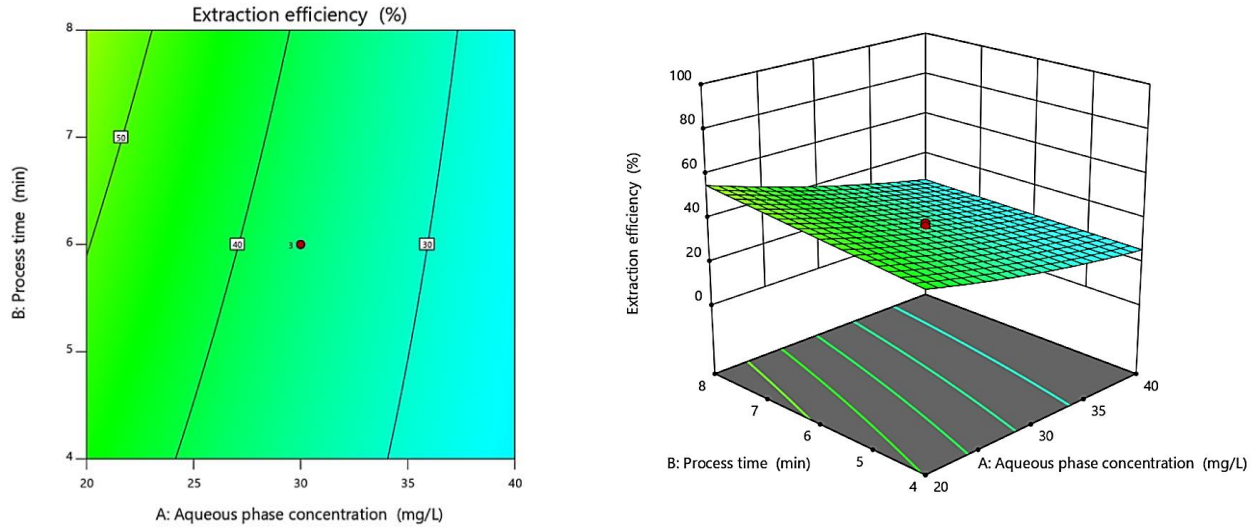
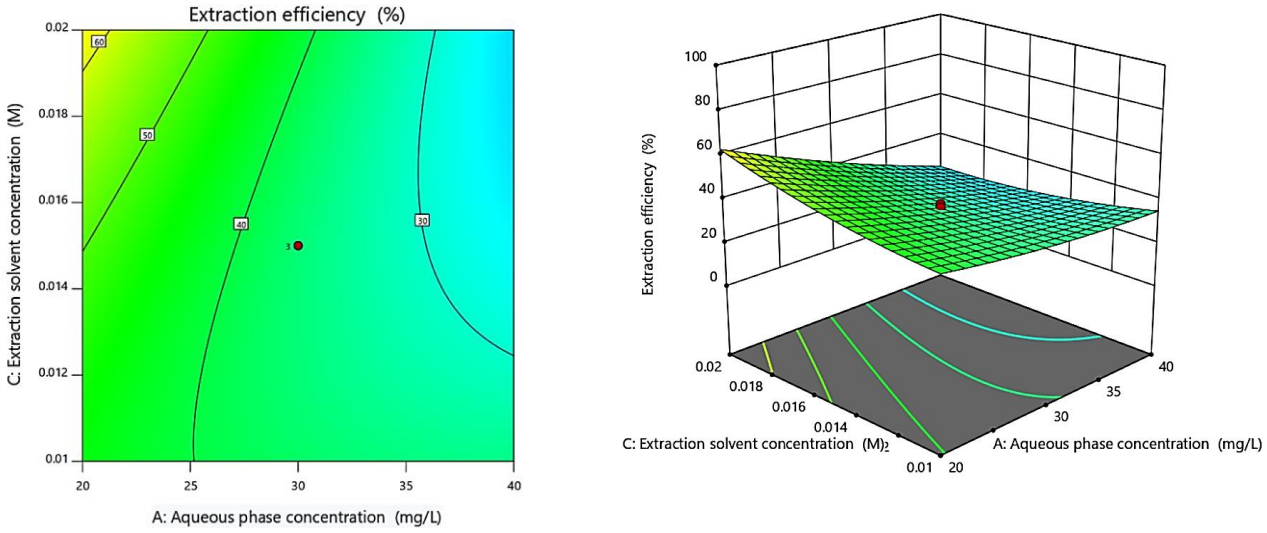

Predicted vs. Actual
Predicted
Actual
0
20
40
60
80
100

Fig. 4. The response levels simultaneously interaction between initial diclofenac concentration in aqueous phase (a) process time, (b) solvent concentration, and (c) centrifuge speed on the DF extraction.

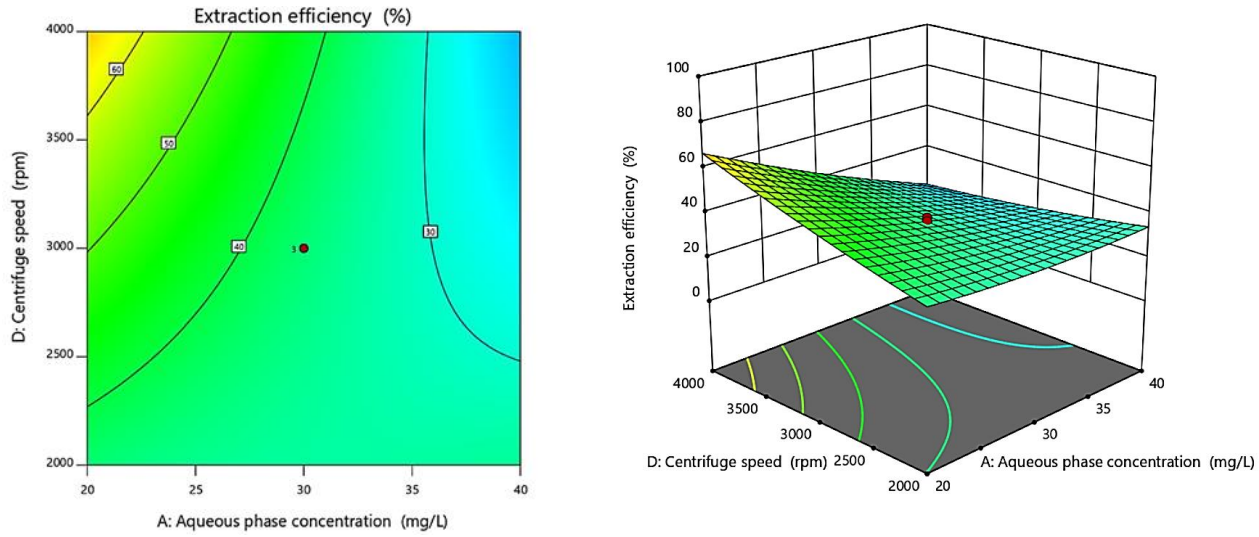
(a)



(b)



(c)



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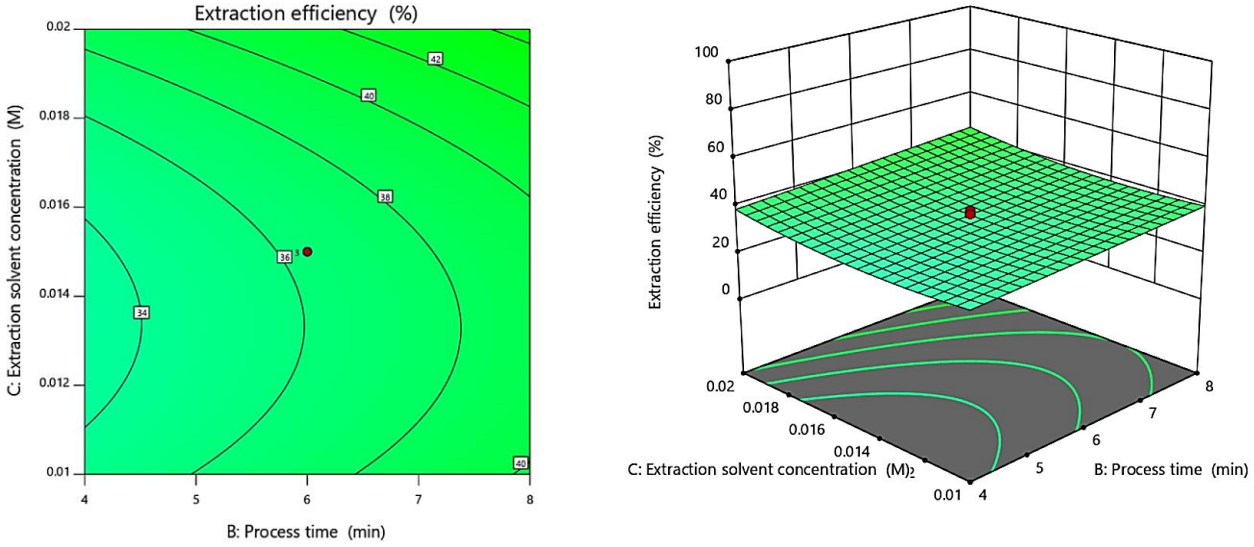
454 Fig. 5. The response levels simultaneously interaction between (a) process time and solvent

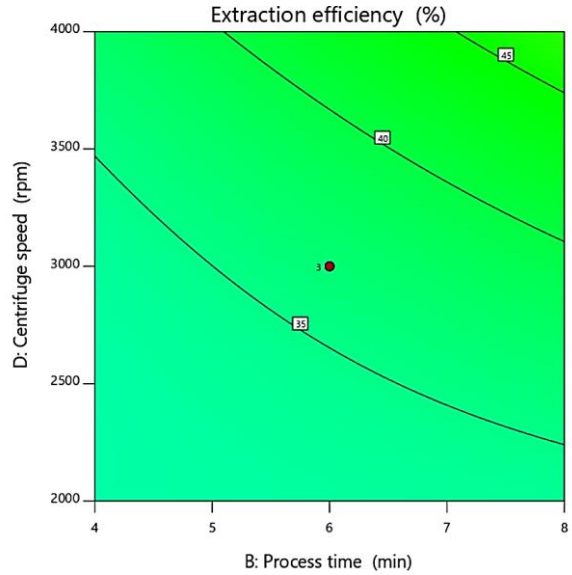
455 concentration, (b) process time and centrifuge speed, and (c) solvent concentration and centrifuge

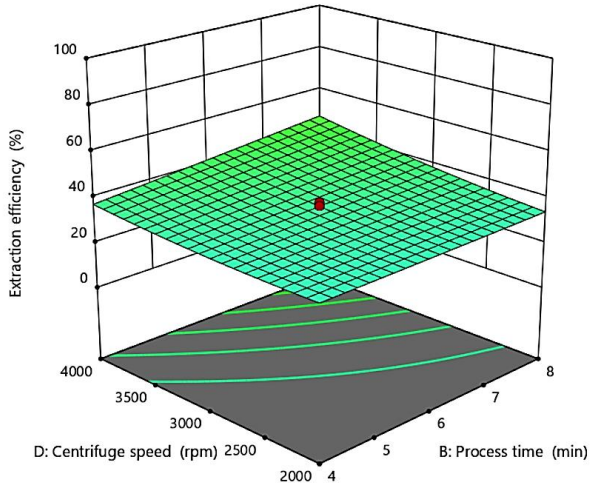
456 speed on the DF extraction.

(a)

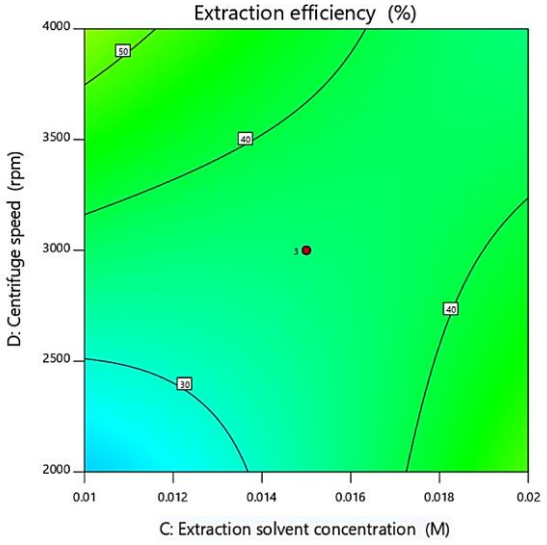


(b)





(c)



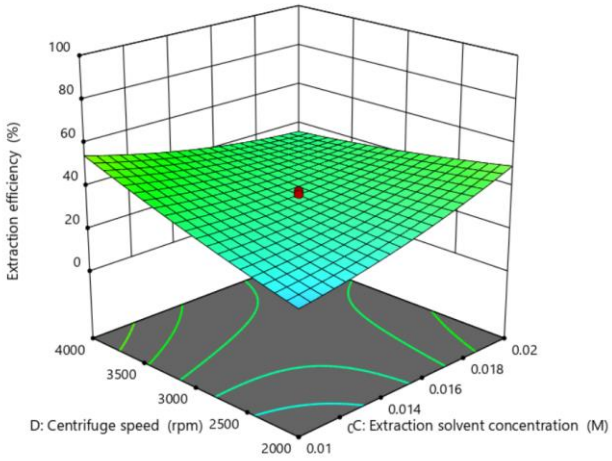


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Table 1. Physical and chemical properties of diclofenac sodium [31].

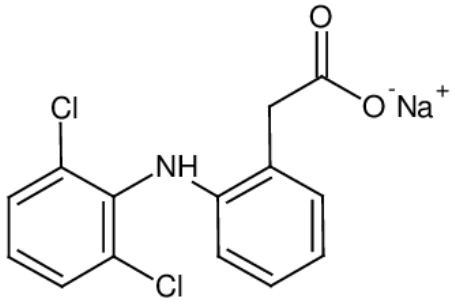
Common name	**Diclofenac sodium**
Melting point	283-285
Molecular weight (g/mol)	318.13
Ionization constant, pK_a	3.99
Molecular structure	

Table 2. The selected ranges and levels in diclofenac extraction efficiency.

Independent variable	Range and levels				
	-2	-1	0	1	2
Diclofenac concentration in aqueous phase (mg/L)	10	20	30	40	50
Process time (min)	2	4	6	8	10
Extraction solvent concentration (M)	0.005	0.01	0.015	0.02	0.025
Centrifuge speed (rpm)	1000	2000	3000	4000	5000

Table 3. Central composite design.

Run	Diclofenac concentration in aqueous phase (mg/L)	Process time (min)	Extraction solvent concentration (mg/L)	Centrifuge speed (rpm)
1	10	6	0.015	3000
2	40	4	0.01	2000
3	30	2	0.015	3000
4	20	8	0.02	4000
5	30	6	0.025	3000
6	40	8	0.02	2000
7	40	4	0.02	2000
8	40	4	0.02	4000
9	40	8	0.01	4000
10	20	8	0.02	2000
11	50	6	0.015	3000
12	20	8	0.01	2000
13	40	8	0.01	2000
14	20	4	0.01	2000
15	20	4	0.02	2000
16	20	4	0.01	4000
17	30	6	0.005	3000
18	30	6	0.015	3000
19	40	4	0.01	4000
20	20	4	0.02	4000
21	30	10	0.015	3000
22	30	6	0.015	3000
23	40	8	0.02	4000
24	30	6	0.015	5000
25	20	8	0.01	4000
26	30	6	0.015	3000
27	30	6	0.015	1000

480 Table 4. Calculated and predicted results of diclofenac extraction efficiency.

Run	Variables				Extraction efficiency (%)	
	A	B	C	D	Experimental	Predict
1	10	6	0.015	3000	68.096	64.86
2	40	4	0.01	2000	31.13	32.87
3	30	2	0.015	3000	34.50	31.16
4	20	8	0.02	4000	77.75	75.52
5	30	6	0.025	3000	53.33	53.03
6	40	8	0.02	2000	38.76	41.61
7	40	4	0.02	2000	39.75	44.55
8	40	4	0.02	4000	8.26	5.29
9	40	8	0.01	4000	46.24	44.47
10	20	8	0.02	2000	65.88	63.46
11	50	6	0.015	3000	25.87	20.39
12	20	8	0.01	2000	19.00	21.50
13	40	8	0.01	2000	27.39	29.77
14	20	4	0.01	2000	14.38	16.11
15	20	4	0.02	2000	56.63	57.92
16	20	4	0.01	4000	68.02	64.68
17	30	6	0.005	3000	46.58	44.63
18	30	6	0.015	3000	34.53	36.42
19	40	4	0.01	4000	33.49	38.84
20	20	4	0.02	4000	60.72	61.25
21	30	10	0.015	3000	41.24	42.33
22	30	6	0.015	3000	36.50	36.42
23	40	8	0.02	4000	9.87	11.07
24	30	6	0.015	5000	47.08	51.13
25	20	8	0.01	4000	80.88	78.81
26	30	6	0.015	3000	38.12	36.42
27	30	6	0.015	1000	39.38	33.09

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Table 5. Analysis of variance for diclofenac liquid-liquid microextraction.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	14	9364.54	668.9	33.58	< 0.0001	significant
A-Feed	1	3409.36	3409.36	171.15	< 0.0001	
B-Time	1	191.08	191.08	9.59	0.0092	
C-TBAB	1	102.87	102.87	5.16	0.0423	
D-Speed	1	480.23	480.23	24.11	0.0004	
AB	1	75.6	75.6	3.8	0.0752	
AC	1	897.3	897.3	45.05	< 0.0001	
AD	1	1798.4	1798.4	90.28	< 0.0001	
BC	1	0.1208	0.1208	0.0061	0.9392	
BD	1	79.48	79.48	3.99	0.069	
CD	1	2064.79	2064.79	103.66	< 0.0001	
A^2	1	82.28	82.28	4.13	0.0649	
B^2	1	0.1166	0.1166	0.0059	0.9403	
C^2	1	204.27	204.27	10.25	0.0076	
D^2	1	42.3	42.3	2.12	0.1707	
Residual	12	239.04	19.92			
Lack of Fit	10	232.57	23.26	7.2	0.1281	not significant
Pure Error	2	6.46	3.23			
Cor Total	26	9603.57				

*df: Degree of fredom

Table 6. Optimal values of parameters and percentage of predicted and experimental extraction.

Operational parameters	The optimal amount	Units
Extractor concentration	0.01	M
The initial concentration of the aqueous phase	20	mg/L
Centrifuge rotation speed	4000	rpm
stay time	8	min

Extraction efficiency	Predicted (%)	Experimental (%)	Error (%)
	78.78	77.91	1.12