Original Article

Application of Solvent Extraction for the Removal of Amoxicillin Drug Residues in Environmental Waters

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Abstract

In this study, removal of amoxicillin ions from aqueous medium by liquid-liquid extraction (LLE) technique was investigated. The LLE process coupled by UV-Visible spectroscopy was carried out by response surface methodology (RSM) based on central composite design (CCD). The process parameters such as extractant concentration, feed acidity, extraction time and diluent type were optimized. At these condition the maximum AMOX extraction was found to be 93.5 % and 96 % using TEA and MDEHPA, respectively. The findings of this study shows that solvent extraction process under the optimum conditions show the considerable potential for environmentally friendly and amoxicillin removal from aqueous media.

Keywords: Amoxicillin, Solvent extraction, Pharmaceutical pollution, Wastewater treatment, Response surface methodology

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1. Introduction

Amoxicillin (AMOX) is a family of β-l actams and is a broad-spectrum penicillin group that is widely used. It is currently one of the most used antibiotics in the world [1]. This drug is useful for the treatment of a number of bacterial infections [2]. It is used to treat many infections such as middle ear infections, sinusitis, sore throat, pneumonia, skin infections, ureteric infections, and chlamydial infections [3]. Most AMOX is excreted unchanged after consumption [4]. For this reason, the possibility of contamination of environmental resources, aquatic and terrestrial ecosystems by these materials have increased [5, 6]. Antibiotics are persistent and lipophilic, and they can remain for a long time because of their continuous entry to the

environment, so that their presence in both low and high concentrations is dangerous [7, 8]. AMOX has toxic effects on organisms in aquatic ecosystems [9]. These combinations cause the destruction of useful and effective microorganisms in biological wastewater treatment processes [10]. AMOX is resistant to biodegradation and it is also hardly decomposed and remains as the active ingredient in urine and feces [11]. Therefore, the conventional purification methods, especially biological purification processes, are not able to eliminate these materials [12].

To date, different methods such as reverse osmosis process (RO) and ion exchange [13, 14], ozonation and advanced oxidation processes [15], nanofiltration [16, 17], fenton process [18, 19], magnetic graphene oxide adsorbent [20], electrocoagulation [21], adsorption on adsorbent materials [22], and supported liquid membrane [10, 23, 24], have been used to remove amoxicillin from the wastewater. Today, the research procedure is focused at finding simple and inexpensive methods that are suited to the same efficiency for use in the treatment of contaminated wastewater and industrial effluents, especially in developing countries which are unable to use costly methods because of economic difficulties.

Liquid–liquid extraction process (LLE), also known as solvent extraction, is a separation method based on components relative solubility in two various immiscible liquids, mostly aqueous and organic solvent. This method is used to extract a solute from one liquid (feed aqueous phase) into other

liquid phase (organic phase). Extraction basically involves of two combining processes: mixing and separating. The following advantages can be mentioned for LLE system: the high operational capability, process simplicity and high efficiency [25, 26]. The solvent extraction has shown a high potential for removal of antibiotics from the aquatic environment. Homsirikamol [27] performed liquid–liquid extraction experiments of AMOX from an aqueous phase into 1-decanol using trialkyl methylammonium chloride (Aliquat 336), di-(2-ethylhexyl)-phosphoric acid (D2EHPA) and tributyl phosphate (TBP) as extractant.

The design of experiments by using RSM as a useful statistical and mathematical tool, is one of the common and new approaches to develop, improve and optimize experimental processes and reducing the number of necessary experiments. The RSM not only determines the optimal level of each parameter but also shows interactions between the parameters and their effect on the response [19].

In the present study, the extraction of AMOX from aqueous solution using teiethylamine and MDEHPA as extractants was done by solvent extraction. The influence of the operating parameters, such as extraction time, extractant concentration and feed phase pH on percentage of AMOX extraction from aqueous solution has been investigated by using response surface methodology (RSM). Also, the effect of various diluents on the removal of AMOX has been studied. Optimization of these factors was performed

by RSM based on central composite design (CCD) to achieve the highest AMOX extraction efficiency.

2. Materials and Methods

The compounds used in the LLE system had analytical grade and were applied without purification. TEA (triethylamine, 99 % purity) and MDEHPA (di-2-ethylhexyl phosphoric acid and mono-2-ethylhexyl phosphoric acid mixture) as extractants for AMOX were obtained from Merck. M2EHPA and TEA structures [28] have been shown in (Figure 1) Toluene ($C_6H_5CH_3$, 99.9 % purity), N-hexane (C6H14, 99.99 % purity), 1-butanol (C4H10O, 99.8 % purity), 2-propanol (C3H8O, 99.5 % purity) and Chloroform (CHCl3, 99 % purity) as diluents was purchased from Merck. Ammonium hydroxide (C6H5CH3, 25 % purity) and hydrochloric acid ($C_6H_5CH_3$, 37% purity) solutions were used to adjust pH and were prepared from the Merck. Sodium nitrite (NaNO2, 97% purity) and para-aminobenzoic acid (C7H7NO2, 99% purity) powders was purchased from Sigma-Aldrich as Amoxicillin detectors. Amoxicillin was kindly donated by Daana Pharmaceutical Company (Tehran, Iran) and was used without more purification. Distilled water was used to make aqueous phase.
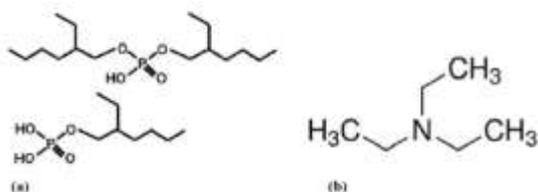

Figure 1. The structures of (a) MDEHPA and (b) Triethylamine.

2.1. Apparatus

A magnetic stirrer type MSH-20D (Germany) was used to mix the aqueous and organic phases. Adjustment of pH was done using pH meter type Pl-700pv (Taiwan). The electronic digital balance type BEL S123 (Italy) was used for weighing. UV–Vis absorption spectrophotometer; type Vario 2600 (Germany) was used for the analysis of AMOX.

2.2. Experiment

Feed solution (AMOX solution) was prepared by dissolving amoxicillin powder in distilled water. In order to study effect of pH on extraction behavior, Feed solution pH was adjusted from 2 to 12 by adding hydrochloride acid or ammonium hydroxide solution. The organic phase was formed by dissolving the desired amount of extractant in the toluene. Five mL of feed solution at a concentration of 100 mg/L was placed into 25 ml glass beaker. Then 5 mL toluene was added to this beaker. The mixture was stirred under room temperature (30 ± 2℃) at 450 rpm for various times (5-25 min). After the extraction process, the mixture was centrifuged at 6000 rpm for 4 minutes to separate aqueous and organic phases. The upper and lower phases were toluene and aqueous solution, respectively. 3 ml from the lower phase (sample) was isolated to measure the AMOX concentration.

2.3. Analytical Method

In this work, analysis of the samples was performed using UV spectrophotometry based on Beer's law calibration plots. 1 ml of sodium nitrite (0.001 M) was poured into a test tube. 1 ml of para-aminobenzoic acid (0.001 M) and

0.5 ml of hydrochloric acid (1 M) were added to this tube. This combination was vortexed for 2 minutes. Then, 3 ml of the extracted specimen was added. Eventually, 1 ml of ammonia solution was poured into it. After 15 minutes, samples were analyzed by spectrophotometer. The maximum absorption of AMOX occurred at 440 nm wavelengths. The calibration curve was determined by analyzing certain concentrations of the feed (0, 5, 10, 15, 20 and 30; (ppm)) (Figure 2). The AMOX concentration was calculated by calibration equation.
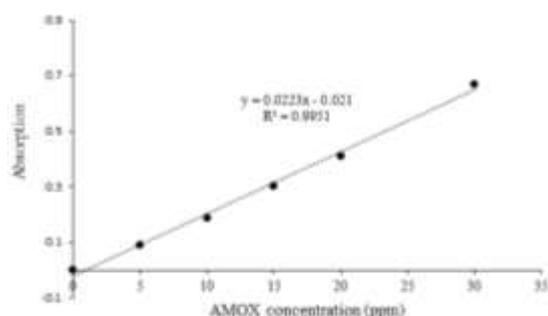

Figure 2. Calibration curve amoxicillin.

2.4. Analytical Response

AMOX extraction efficiency was obtained by using Equation 1.

Extraction (%) $= \frac{[AMOX]_i - [AMOX]_f}{[AMOX]_i} \times 100$ (1)

Where, $[AMOX]_i$ and $[AMOX]_f$ is the concentration of AMOX ions in aqueous phase before and after extraction, respectively.

2.5. Experimental Design

A set of experiments was carried out in accordance with the experimental design obtained from the Design-Expert 10.0.6 software and the central composite design (CCD) in order to optimize the AMOX extraction efficiency with TEA and MDEHPA. Three variables, namely feed solution pH, extractant concentration and extraction time, were investigated at five levels. The coded and uncoded levels for each parameter are listed in (Table 1). In this study, 20 tests were performed according to the conditions mentioned in (Table 2). Experiment was repeated 6 times at the center point. Experimental extraction results (response) are given in (Table 2). A model that is a quadratic equation was developed to describe the relationship between AMOX extraction efficiency and three parameters as defined by Equation 2:

$Y = \alpha_0 + \sum_{i=1}^{m} \alpha_i X_i + \sum_{i=1}^{m} \alpha_{ii} X_i^2 + \sum_{i<j}^{m} \sum_{j}^{m} \alpha_{ij} X_i X_j$ (2)

Where Y is the predicted extraction percent of AMOX. X_i And X_j are the actual values of the independent parameters. α_i, α_{ii} And α_{ij} are the effects coefficients of linear, second degree, and binary interactions on the response which are estimated by regression. These coefficients were obtained by ANOVA. α_0 Is the constant value. Three-dimensional graphs were plotted to observe the effects of variables and their interactions on AMOX extraction.

Table 1. Experimental range and levels of independent variables in coded and un-coded forms.

Variable	Levels				
	-2	-1	0	1	2
Feed solution pH, A	2	4.5	7	9.5	12
Extractant concentrateon, % (V/V), B	1	4	7	10	13
Extraction time, (min), C	5	10	15	20	25

Table 2. CCD for the experiments of AMOX extraction based on the coded form.

Run	Factors			Extraction efficiency (%)	
	A	B	C	Triethylamine	MDEHPA
1	0	-2	0	69.2	65.6
2	0	0	-2	73.7	73.0
3	2	0	0	80.1	90.0
4	1	-1	1	77.2	74.4
5	-1	-1	1	78.0	64.0
6	-2	0	0	81.5	63.7
7	-1	1	1	87.1	73.3
8	0	0	2	81.8	74.1
9	-1	-1	-1	69.2	64.1
10	0	0	0	80.0	74.3
11	0	0	0	80.0	74.3
12	0	-1	0	80.0	78.4
13	1	2	-1	69.3	72.2
14	0	1	0	92.5	80.2
15	0	0	0	80.0	74.3
16	0	0	0	80.0	74.3
17	1	1	1	87.3	85.4
18	-1	1	-1	82.4	72.2
19	0	0	0	80.0	74.3
20	1	1	-1	82.1	88.3

Table 3. ANOVA for response surface quadratic model for the percentage extraction of amoxicillin using Triethylamine as extractant.

Source	Sum of Squares	df	Mean Square	F value	P value	Remark
Model	661.22	9	162.43	73.48	< 0.0001	significant
A	0.81	1	164.85	0.81	0.3892	
B	526.70	1	163.80	526.79	< 0.0001	
C	114.49	1	180.95	114.51	< 0.0001	
AB	0.045	1	10.40	0.045	0.8363	
AC	0.020	1	77.00	0.020	0.8903	
BC	5.78	1	5.625E-003	5.78	0.0370	
A^2	0.42	1	376.13	0.42	0.5306	
B^2	0.51	1	1051.17	0.51	0.4926	
C^2	10.07	1	121.32	10.07	0.0099	
Residual	10.00	10	1.05			
Lack of Fit	10.00	5	1.30			
Pure Error	0.000	5	0.57			
Cor Total	671.22	19				
Std. Dev.	1.00		R-Squared	0.9851		
Mean	79.57		Adj R-Squared	0.9717		
C.V. %	1.26		Pred R-Squared	0.8776		
PRESS	82.15		Adeq Precision	32.459		

3. Results and Discussion

3.1. Regression Model for the AMOX Extraction System with TEA

The coefficients of quadratic Equation 2 was obtained from ANOVA. It is shown in Equation 3.

$$Y_1 = +46.477 - 0.169A + 2.413B + 1.997C + 0.016AB - 0.010AC - 0.058BC + 0.009A^2 + 0.020B^2 - 0.032C^2 \quad (3)$$

Where Y_1 is the percent of AMOX predicted extraction using triethylamine, A, B and C are feed solution pH, triethylamine concentration and extraction time, respectively. As shown in (Figure 3(a)), there is a good match between the predicted extraction and the actual amount ($R^2 = 0.9851$, n=20). Therefore, the Equation 3 provided by the RSM is able to predict the percentage of AMOX extraction. The results of ANOVA are shown in (Table 3). The model F-value of 70.59 and p-value of less than 0.0001 indicates that the model is absolutely significant. As reported in (Table 3), B, C, BC and C^2 are the influential parameters of the model. Equation 3 is summarized as Equation 4 by eliminating parameters and interactions that are not noticeable.

$$Y_1 = +46.477 + 2.413B + 1.997C - 0.058BC - 0.032C^2 \qquad (4)$$

3.2. Regression Model for the AMOX Extraction System with MDEHPA

The coefficients of quadratic Equation 2 was also obtained for the tests done by MDEHPA. It is shown in Equation 5.

$$Y_2 = +50.095 + 0.054A + 1.488B + 0.571C + 0.166AB - 0.020AC - 0.033BC + 0.110A^2 - 0.043B^2 - 0.005C^2 \qquad (5)$$

Where Y_2 is the percent of AMOX predicted extraction using MDEHPA, A, B and C are feed solution pH, MDEHPA concentration and extraction time, respectively. There is a good match between the predicted extraction and the actual extraction ($R^2 = 0.9809$, n=20) as shows in (Figure 3(b)). Therefore, the Equation 5 provided by the RSM is able to predict the percentage of AMOX extraction.
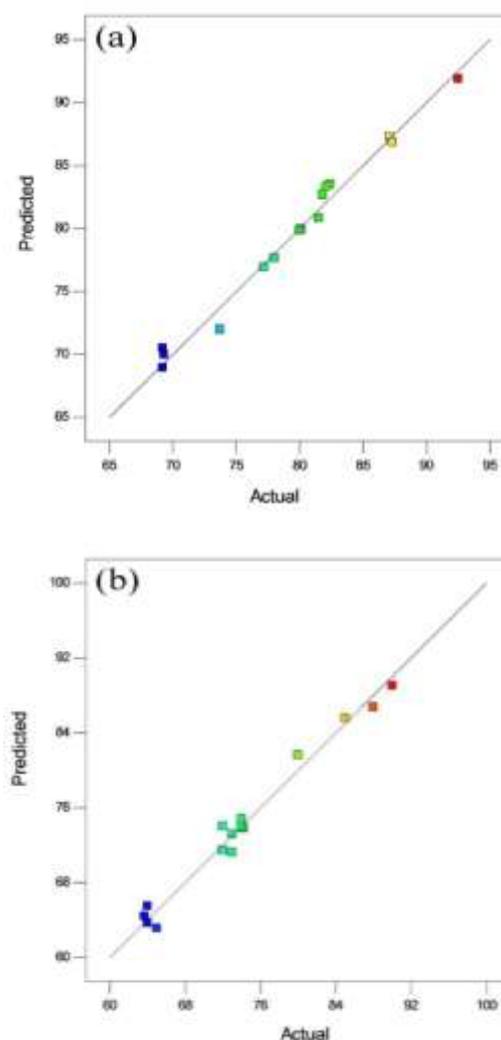

Figure 3. Predicted efficiency of AMOX extraction versus actual values for (a) TEA and (b) MDEHPA extractant.

The results of ANOVA are shown in (Table 4). The model F-value of 55 and p-value of less than 0.0001 indicates that the model is absolutely significant. As presented in (Table 4), A, B, AB and A^2 are the influential parameters of the model. Equation 5 is summarized as Equation 6 by eliminating parameters and interactions that are not noticeable.

$$Y_2 = +50.095 + 0.054A + 1.488B + 0.166AB + 0.110A^2 \qquad (6)$$

Table 4. ANOVA for response surface quadratic model for the percentage extraction of amoxicillin using MDEHPA as extractant.

Source	Sum of Squares	df	Mean Square	F value	P value	Remark
Model	985.87	9	109.54	54.56	< 0.0001	significant
A	607.62	1	607.62	302.62	< 0.0001	
B	342.25	1	342.25	170.45	< 0.0001	
C	0.36	1	0.36	0.18	0.6809	
AB	12.50	1	12.50	6.23	0.0317	
AC	0.50	1	0.50	0.25	0.6286	
BC	2.00	1	2.00	1.00	0.3418	
A^2	12.00	1	12.00	5.98	0.0346	
B^2	3.95	1	3.95	1.97	0.1908	
C^2	0.37	1	0.37	0.19	0.6761	
Residual	20.08	10	2.01			
Lack of Fit	20.08	5	4.02			
Pure Error	0.000	5	0.000			
Cor Total	1005.95	19				
Std. Dev.	1.42		R-Squared	0.9800		
Mean	74.09		Adj R-Squared	0.9621		
C.V. %	1.91		Pred R-Squared	0.8393		
PRESS	161.61		Adeq Precision	25.874		

3.3. Effect of Parameters on AMOX Extraction Efficiency

3.3.1. Effect of Feed pH

The batch extraction of AMOX was done by using various concentrations of the described extractants (TEA and MDEHPA) dissolved in toluene and changing the pH of AMOX solution ranging from 2 to 12. Results of AMOX extraction (Figure 4) indicated that the highest extraction for MDEHPA surprisingly occurred in pH 12. Although AMOX is anionic in this pH and should be repelled with the MDEHPA negative charge. The probable reason was that solvation were created, and resulted in more complexes formation compared to those formed from the ion pair [27]. In the case of TEA, the change in pH of feed solution did not change the extraction performance, and a relatively stable extraction percentage was observed.
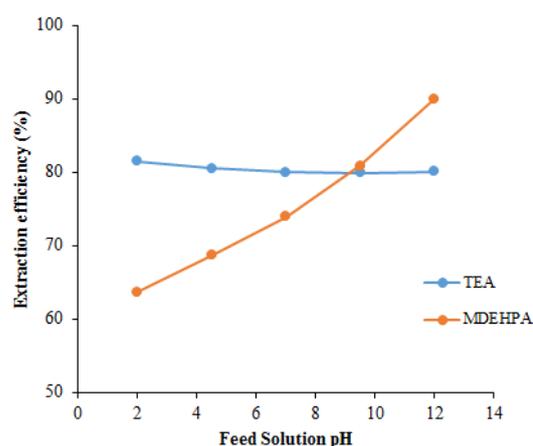

Figure 4. Effects of feed solution pH on the AMOX extraction (extractant concentration: 7 %(V/V); extraction time: 15 min; agitation speed: 450 rpm; W/O ratio: 1.)

3.3.2. Effect of Extractant Concentration

The influence of extractant concentrations on AMOX removal efficiency were evaluated. The concentrations of TEA and MDEHPA were changed from 1 to 13 % (V/V). (Figure 5) shows that with the increase in the extractant percentage in the organic phase, the amount of AMOX extraction increased for both the TEA and MDEHPA. Increasing the amount of extraction due to the increase in the

concentration of the extractant could be confirmed by the forward change of the reaction according to the Le Chatelier's principle when adding extra extractants [27] In fact, by increasing of TEA and MDEHPA concentrations, the ability to extract of AMOX increased.
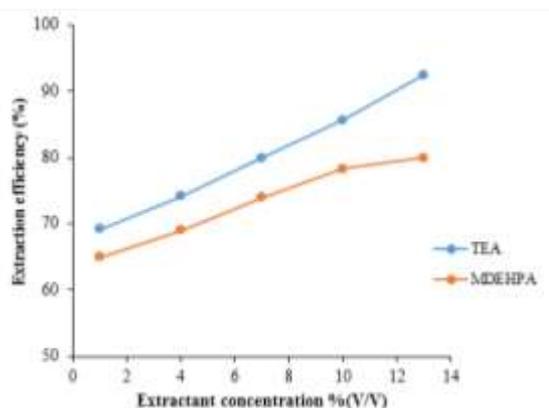

Figure 5. Effects of extractant concentration on the AMOX extraction (feed solution pH: 7; extraction time: 15 min; agitation speed: 450 rpm; W/O ratio: 1).

3.3.3. Effect of Extraction Time

The extraction time (agitation time) was varied from 5 to 25 min to evaluate its effect on the AMOX extraction percentage. Based on (Figure 6) the extraction time had a considerable effect on the AMOX removal with TEA. The reason is that by increasing the extraction time, the contact time of the aqueous and organic phases increases, which leads to an increase in the extraction efficiency [29, 30]. Finally, the equilibrium between the two phases is created and thus the removal efficiency does not change with the further increase in the extraction time. It can be seen that the extraction efficiency with MDEHPA is little affected by extraction time.
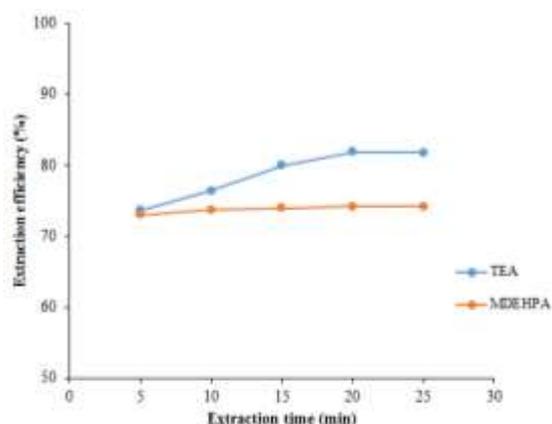

Figure 6. Effects of extraction time on the AMOX extraction (extractant concentration: 7 %(V/V); feed solution pH: 7; agitation speed: 450 rpm; W/O ratio: 1).

3.3.4. Effect of Diluents

The effect of type of organic solvents (N-hexane, 2-propanol, 1-butanol, toluene and chloroform) on the amount of AMX extraction was studied and the results are shown in (Figure 7). As it was observed, the highest extraction efficiency was obtained using toluene among the solvents used. Maximum uptake was observed for toluene which may be attributed to very good solubility of the AMOX complex in the aromatic solvents.
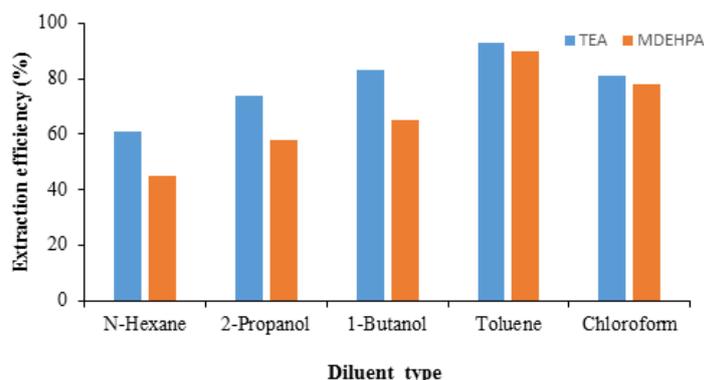

Figure 7. Influence of diluent type on the AMOX extraction.

3.4. Optimization of Process Parameters for the AMOX Extraction Using Triethylamine and MDEHPA Extractants

The 3D graphs of the effect of the factors on the amount of AMOX extraction were plotted by the provided Equations (3 and 5) by changing the values of the two factors from the levels -2 to 2 and keeping the remaining factors at their zero levels as illustrate in (Figure 8-10). (Figure 8 & 10(a)) shows the interaction between the extraction time and the value of TEA. This plot exposes that optimal TEA concentration is around 12–13 %(V/V) and the optimal extraction time is in the range of 13–25 min. The interaction between the solution pH and the concentration of MDEHPA was observed in (Figure 9 & 10(b)). The optimal MDEHPA concentration is around 12–13 % (V/V) and the optimal pH solution is in the range of 10-12 min.

The values of these three factors were optimized by the Design Expert 10.0.6 software for both experimental sets. In the software optimization section, 100 different solutions with having an AMOX extraction percentage from 90 to 95 were obtained. Among these solutions, the one that had the lowest extractant concentration and the extraction time due to economic significance was selected. The optimum actual (uncoded) amounts for TEA were: Feed solution pH – 2.7, TEA concentration – 12.9 % (V/V) extraction time – 19 min and for MDEHPA were: Feed solution pH – 11, TEA concentration – 12.3 % (V/V) extraction time – 21 min, respectively. In these conditions, the AMOX extraction efficiency predicted by the model for TEA and MDEHPA extractants was %93.5% and %96.

3.5. Validation of Results

In recommended optimum operating conditions a validation test was conducted to evaluate the suitability and adequacy of the model equation. The result of the experimental extraction was compared with the predicted extraction by the model and was reported in (Table 5). The relative error value is less than 3%, which confirms the proper modeling and shows that the optimization objective has been fulfilled.
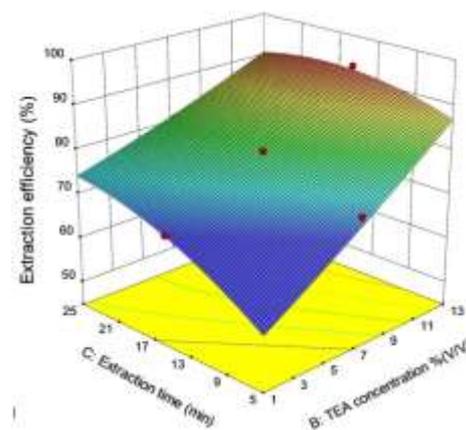

Figure 8. Response surface plot for AMOX extraction; the interaction between TEA concentration and extraction time.
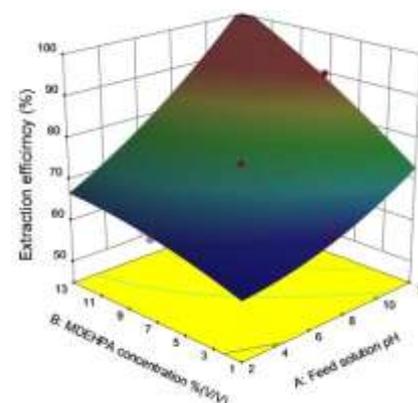

Figure 9. Response surface plot for AMOX extraction; the interaction between MDEHPA concentration and feed solution pH.

Table 5. Validation tests results**.**

Terms		Optimum condition	
		Triethylamine	MDEHPA
Parameters	Extractant concentration %(V/V)	2.7	11
	Feed phase pH	12.9	12.3
	Extraction time (min)	19	21
Results	Predicted extraction efficiency (%)	92.5	96
	Experimental extraction efficiency (%)	90.1	93.4
	% Error	2.59	2.7
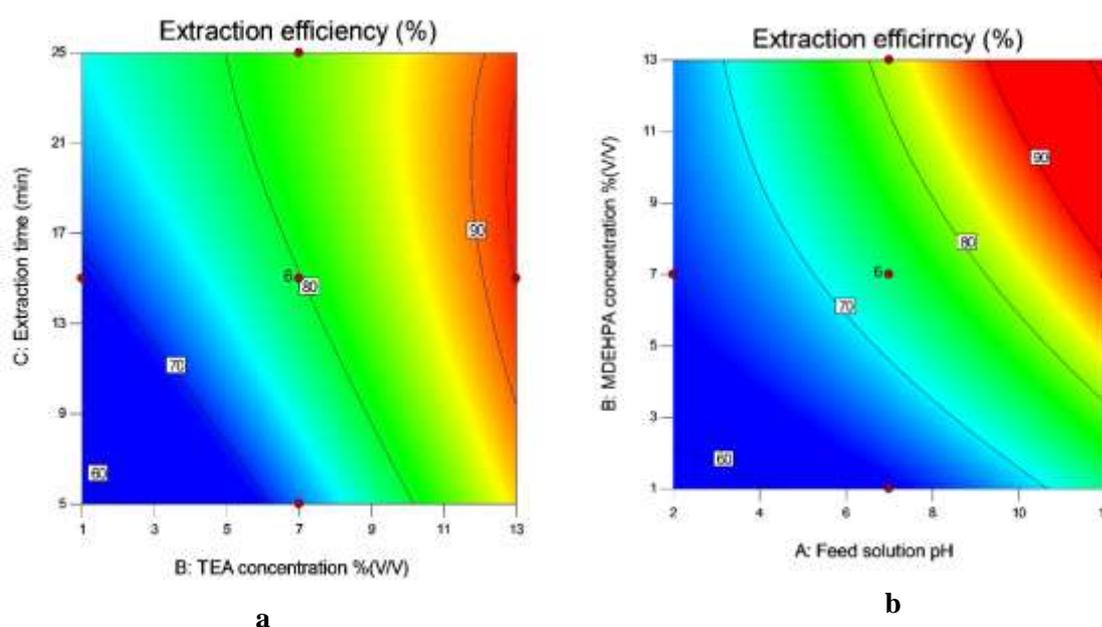
Figure 10. Contour plots for AMOX extraction; (a) the interaction between TEA concentration and extraction time, (b) the interaction between MDEHPA concentration and feed solution pH.

4. Conclusion

The aim of this study was to extend the process of liquid-liquid extraction (LLE) for the extraction of amoxicillin from aqueous solution. The organic phase consisted of triethylamine and MDEHPA as extractants and toluene as diluent. The influence of various parameters such as extractant concentration, feed solution pH and extraction time on the percent of AMOX extraction were studied. RSM was applied to detect the optimum process conditions. The mounts of quadratic predicted by model were found to differ with R^2 value of 0.9851 and 0.9124 for Triethylamine and MDEHPA, respectively. The best operating conditions for triethylamine were: pH – 2.7, extractant concentration – 12.9 % (V/V) and extraction time – 19 min and for MDEHPA were: pH – 11, extractant concentration – 12.3 %(V/V) and extraction time – 21 min. In these conditions, the maximum removal efficiency for the TEA and

MDEHPA extractants was %93.5% and %96, respectively. The effect of solvent type on extraction was also investigated and it was found that toluene was a suitable solvent for this process.

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