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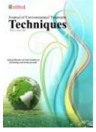

Application of Response Surface Methodology for Optimization of Cefixime Removal from Aqueous Solutions by Granular Ferric Hydroxide

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Abstract

In general, very limited information is available on the adsorption of antibiotics by granular ferric hydroxide (GFH) in an aqueous solution. In order to gain an understanding of the adsorption process of cefixime by GFH, this study was conducted in a controlled batch system and using central composite design by response surface methodology (RSM). The effects of pH, initial Cefixime concentration, adsorbent dose and contact time on the adsorption rates of cefixime were investigated. The results of optimization of the variables derived in the initial pH = 6, cefixime concentration were 8 mg L^{-1}, adsorbent dosage = 1 g L^{-1} and contact time = 50 min, and maximum removal efficiency of 99.63%. According to RSM, this study follows the Quadratic model ($R^2 = 0.970$). Considering the good quality, economic and feasibility aspects, adsorption of CFX with GFH is recommended as a successful method of CFX removal from various aqueous solutions.

Keywords: Adsorption, Cefixime, Granular ferric hydroxide, Aqueous solution

1 Introduction

Antibiotics are a large and diverse group of Pharmaceuticals compounds, which are widely used in medicine, veterinary medicine and agriculture. These compounds are not fully metabolized in the body after use [1] And they enter aquatic environments from various point and non-point sources such as sewage, waste and agricultural runoff [2]. These compounds play an important role in infectious disease treatment [3; 4]. But, Because of the widespread diversity and use and antibiotic resistance, they are recognized as the most important emerging pollutants in the aquatic environment [5-8]. Although their detected value is trace levels (ng/L to low µg/L), [9] But even that, low concentration levels can cause irreversible effects such as carcinogenesis, mutagenesis, disruption of endocrine and emergence of antibiotic-resistant genes and damage to DNA and lymphocytes [10-12]. Therefore, the presence of these compounds in water, especially drinking water sources, poses a serious threat to human health and the environment. Therefore, investigation, monitoring and removal of these compounds from aquatic environments are important requirements that can have a significant impact on water quality [2]. CFX is one of the third generation antibiotics of cephalosporin [13; 14]. This compound can be used against pathogens such as anaerobic bacteria, Enterobacteriaceae, gram-negative strains such as Escherichia coli, Klebsiella, Hemophilus influenza, Serratia and etc. [15]. Therefore, this drug used to treat a wide range of infections such as respiratory infections, gonorrhea, otitis media, throat inflammation, bronchitis, and urinary tract infections [16; 17]. After consume of CFX, about 40-50% can be absorbed by gastrointestinal tract and around 50% is excreted in the aquatic environment by urine [1]. Due to the harmful effects of these compounds as well as their cumulative and non-biodegradable properties, their removal from the sewage is necessary [18]. However, conventional biological treatment methods can eliminate less than 20% of these pollutants. Therefore, researchers are looking for suitable alternative methods for the treatment of pharmaceutical wastewater. Biological removal methods are a cost-effective method but have little effect on resistant organic compounds. Chemical and physical treatment can produce high efficiency and produce high quality wastewater but its treatment costs are relatively high [19]. However, the adsorption method, which is a physical method, is one of the most widely used methods for removal of aquatic pollutant [20; 21]. Studies show that iron and aluminum oxides have an important role in the absorption of pollutants. The University of Berlin (Germany) has introduced a new adsorbent called granular iron hydroxide (GFH) [22]. GFH is among excellent adsorbents for impurities in water, which having a high porosity and suitable sites smaller than 4.5 microns [23]. The adsorbent of GFH had favorable results in the removal of arsenic [24], fluoride [23], bromate [25], phosphate [26], perchlorate [27] and other natural organic matter [25]. According to searches, it seems that GFH has not yet been used to absorb pharmacological compounds from aquatic environments. On the other hand, in a report published

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by the World Health Organization in 2019 on the rate of antibiotic consumption, CFX was introduced as one of the most widely used antibiotics [28]. Therefore, the researchers decided to investigate the efficacy of GFH in the absorption of cefixime antibiotics. In this study, effective parameters in the adsorption process, including pH, initial CFX concentration, adsorbent dose and contact time were first investigated using response surface methodology (RSM).

2 Materials and Methods

2.1 Chemicals

In this study, All the employed chemical compounds were of laboratory grade. CFX 98% with molecular formula $C_{16}H_{15}N_5O_7S_2$;453.45 mol.wt were purchased from sigma Aldrich Co.(USA). Hydrochloric acid, Sodium hydroxide and methanol, were purchased from Merck Company.

2.2 Preparation of GFH

GFH was purchased from Wasserchemie GmbH & Co. Table 1 demonstrates the characteristics physical and chemical of GFH. In order to remove moisture, GFH granules was placed in the oven at 105°C for 90 min and also, placed in the desiccator for cooling [29].

Table 1: The characteristics of GFH

Character	**Value**
Specific surface area (m^2/g)	280
Particle size (mm)	0.32 - 2
Water content	43 - 48
pH_{pzc}	7.5 – 8.2
Bulk density (kg/m^3)	1250
Porosity of grains (%)	72 - 77

2.3 Experimental design

RSM is a combines of efficient mathematical approaches and statistical powerful technique that are used to the modeling and analysis of design parameters on the desired value of the response function [30]. also, it is used to minimize the number of experiments for optimization studies in chemical and biochemical processes [31]. In this study, a central composite design (CCD) used for optimization and statistical analysis of four factors solution pH (A), initial CFX concentration (B), GFH dose (C) and Reaction time (D). Each factor was examined at five levels i.e. (-α, -1, 0, +1 and +α) (Table 2) and the model was designed with 30 runs along the levels as given in Table 3. In this work, Analysis of variance (ANOVA test) was used to the multiple regression analysis of the model and response surface graphs were done by using Design- Expert, version 7.1.6.

2.4 Adsorption experiment

After preparation of the GFH, desired concentrations were prepared based on 1 mg/L CFX stock solution and the adsorption experiments were carried out according to the RSM matrix (Table 3). Each run of experiment, a volume of 10 mL CFX solution in Erlenmeyer flasks was prepared. The pH of the samples was adjusted using 1 N solutions of HCl or NaOH and measured by pH7110 (WTW). In the following, Samples were placed in a shaker incubator at 200 rpm to be mixed. After elapse of contact time, samples were Centrifuge 5804 (Eppendorf) for 20min at 4000 rpm to separate the adsorbent. The CFX concentration was determined by spectrophotometer (T80 UV/VIS, PG Instruments Ltd) within the wavelength of 288.5 nm [32] and removal efficiency of CFX was calculated by Eq. 1.

$$R\% = \frac{(C_0 - C_t)}{C_0} \times 100 \qquad (1)$$

where C_0 and C_t are the initial and final concentration of CFX in solution (mg/l), respectively.

Table 2: Coded and actual values of numeric factors

Factor (unit)	Code	level				
		$-\alpha$	-1	0	+1	$+\alpha$
Solution pH	X_1 (A)	3	4.5	6	7.5	9
Initial CFX concentration (mg/l)	X_2 (B)	1	4.5	8	11.5	15
GFH dose (g/l)	X_3 (C)	0	0.5	1	1.5	2
Reaction time (min)	X_4 (D)	5	27.5	50	72.5	95

2 Results and Discussion

3.1 Statistical analysis

The CCD was used to determine the correlation of four independent factors (pH (A), CFX concentration (B), GFH dosage (C), and contact time (D)) in removal of CFX by GFH. The CCD selected the Quadratic model as the best fitted model for this study. This model is presented in Eq. 2.

$$R\ (\text{CFX reduction efficiency (\%)}) = +93.14 - 2.71 *A - 1.16 *B + 16.04 *C + 7.41 *D + 2.28 *A\ B + 3.69 *A\ C - 8.04 *C\ D - 10.12 * C^2 - 5.31 * D^2 \qquad (2)$$

As shown in Table 4, analysis of variance (ANOVA) indicate that there is a significant relationship between independent variables and the removal efficiency of CFX. Also, The Model F-value of 72.15 implies the model is significant and there is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. According to Table 4, In this case A, C, D, AC, CD, C^2, D^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. Also, the F-value for Lack of Fit is 3.46 which indicate the relationship between Lack of Fit and pure error is not significant. Additionally, determination coefficient "R-Squared" of 0.639, "Pred R-Squared" of 0.9134 and "Adj R-Squared" of 0.9567 is in reasonable agreement which determine the quality of polynomial model. "Adeq Precision" measures the signal to noise ratio of the study. A ratio greater than 4 is desirable and indicate this model can be used to navigate the design space which in this work, ratio of 30.839 indicates an adequate signal.

The coefficient of variation (CV) indicates the degree of precision and credibility of the result. It is the ratio of the standard deviation to the average of data (sd/mean) and is a good measure of relative variability of the experiments. [33] In general, a lower the value of the CV % (<10%) means the smaller level of dispersion around the mean [34]. In this study, a small value of CV (5.42) and standard deviation (4.38) indicates greater reliability of the model.

Table 3: Central composite designed experiments and obtained and predicted responses

Run Order	pH	CFX Concentration (mg/l)	GFH dose (g/L)	Time (min)	Removal Efficiency (%)		
					Obtained	Predicted	Residual
1	6	8	1	50	94.92	93.14	1.78
2	7.5	11.5	0.5	27.5	43.53	40.93	2.61
3	4.5	4.5	1.5	72.5	97.40	95.57	1.83
4	4.5	4.5	0.5	72.5	86.63	86.96	-0.33
5	7.5	11.5	1.5	27.5	96.53	96.47	0.06
6	7.5	11.5	0.5	72.5	68.14	71.83	-3.69
7	6	8	2	50	88.81	84.73	4.08
8	6	8	1	50	91.86	93.13	-1.27
9	4.5	11.5	1.5	27.5	94.30	89.95	4.35
10	6	8	1	50	94.36	93.13	1.23
11	6	8	1	95	90.48	86.70	3.77
12	6	8	1	50	93.81	93.13	0.67
13	6	8	0	50	15.65	20.57	-4.92
14	6	8	1	5	52.45	57.06	-4.61
15	3	8	1	50	96.39	98.55	-2.16
16	4.5	11.5	0.5	72.5	85.27	80.07	5.20
17	7.5	4.5	0.5	72.5	69.56	69.60	-0.03
18	4.5	4.5	1.5	27.5	93.49	96.84	-3.35
19	4.5	4.5	0.5	27.5	60.78	56.06	4.72
20	6	8	1	50	94.08	93.13	0.95
21	9	8	1	50	85.63	87.71	-2.08
22	7.5	4.5	1.5	27.5	93.70	94.24	-0.53
23	4.5	11.5	0.5	27.5	44.96	49.17	-4.21
24	6	1	1	50	89.82	95.46	-5.64
25	7.5	4.5	1.5	72.5	89.92	92.97	-3.05
26	7.5	11.5	1.5	72.5	95.02	95.20	-0.18
27	4.5	11.5	1.5	72.5	82.22	88.68	-6.46
28	7.5	4.5	0.5	27.5	45.11	38.69	6.42
29	6	15	1	50	89.16	90.81	-1.65
30	6	8	1	50	99.63	93.13	6.50

3.2 The Influence of variables and their interactions on pollutant level

3D contours and perturbation plots were used to evaluate the effect of variables on the efficiency of cefixime removal process by GFH. As shown in Fig 1, the perturbation plot was used for compares the effect of dependent factors at a particular point in the design space. In this graph, the slope of each line indicates the sensitivity of that factor in adsorption process. According fig 1 the factors C (GFH dose) and D (reaction time) had the greatest impact. In Eq 2, dose of GFH, with coefficients of 16.04 have the most effects on the removal of CFX (%).3D contours in Fig. 2-a and 2-b show the interaction between of GFH dosage with reaction time and pH on CFX removal efficiency. As shown in Fig 2-a, increasing the GFH dosage from 0.5 to 1.5 g/l and increasing the reaction time from 27.57 to 72.5 min increased CFX adsorption efficiency. The fast removal efficiency of the early stages can be attributed to the presence of more active sites on the GFH surface which an increase in GFH dosage can increase active surface places and provided a wider contact area between CFX and GFH Nevertheless, these sites become saturated over time and, on the other hand, the removal efficiency decreases due to the repulsive force between the ions adsorbed on GFH and the soluble phase ions [35, 36]. Amarai obtained similar results with the interaction of time and dosage parameters on the removal of ciprofloxacin and amoxicillin, which is consistent with the present study [37].

Table 4: The analysis of variance (ANOVA) for adsorption of CFX on GFH

Source	Sum of Squares	df	Mean Square	F-Value	p-value	
Model	12454.49	9	1383.83	72.15	< 0.0001	Significant
A-pH	176.34	1	176.34	9.19	0.0066	
B-CFX(mg/l)	32.57	1	32.57	1.70	0.2074	
C-GFH Dos(g/l)	6173.00	1	6173.00	321.83	< 0.0001	
D-time(min)	1317.46	1	1317.46	68.69	< 0.0001	
AB	83.20	1	83.20	4.34	0.0503	
AC	217.97	1	217.97	11.36	0.0030	
CD	1053.29	1	1035.29	53.97	< 0.0001	
C^2	2913.51	1	2913.51	151.90	< 0.0001	
D^2	802.81	1	802.81	41.85	< 0.0001	
Residual	383.62	20	19.18			
Lack of Fit	349.92	15	13.33	3.46	0.0882	Not significant
Pure Error	33.70	5	6.74			
Cor Total	12838.11	29				
R-Squared				0.9701		
Adj R-Squared				0.9567		
Pred R-Squared				0.9134		
Adeq Precision				30.839		
Coefficient of variation (%)				5.42		
standard deviation				4.38		

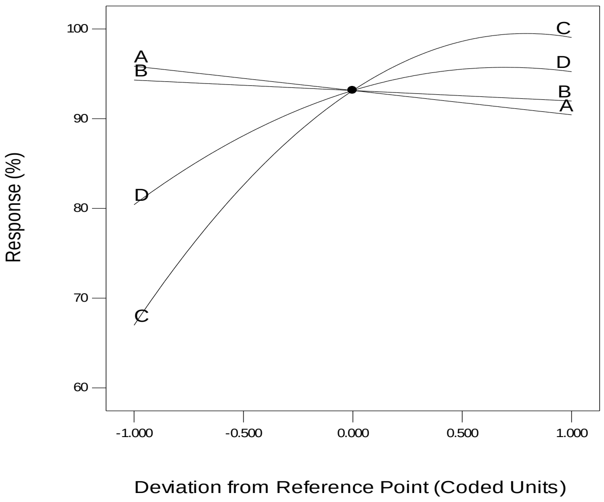

Figure 1: Perturbation plots for CFX reduction efficiency (A) pH, (B) Initial concentration, (C) GFH dose and (D) contact time

Diagram 2-b also shows the interaction between pH and GFH dosage. With increasing adsorbent dose and decreasing pH from 7.5 to 4.5 the adsorption efficiency increased from about 60% to <99%. The surface properties of CFX ions is pH dependent. The CFX ionizing molecule has two carboxyl groups (pKa is 3.73 and 1/2).[38] The surface properties of CFX ions is pH dependent. The CFX ionizing molecule has two carboxyl groups (pKa is 3.73 and 1/2). At higher pH < 3.37 it is mainly CFX in the form of negative ions. On the other hand, the isoelectric point (pHpzc) is an important factor for surface charge, when the pH is lower than pHpzc, the surface charge of GFH is usually positive and the higher than pHpzc is negative charge. Therefore, in pH below 7.5, the GFH surface charge was positive and CFX charge was mostly in the form of a negative charge. Thus, by electrostatic interactions, CFX negative ions are adsorbed on the positive surface of GFH.

The interaction between pH and initial CFX concentration is shown in Fig 2-c. According to the fig 2-c, the removal efficiency decreased with increasing initial concentration from 4.5 to 11.5 mg/L and increasing pH from 4.5 to 7.5. This decrease in removal efficiency at concentrations higher than CFX can be attributed to the saturation and reduction of active sites present on the GFH surface [36; 39]. Similar results were obtained in the study of Omrane et al [40].

4 Conclusions

In this study, the adsorption of CFX on GFH from aqueous solutions was investigated. The RSM method based on CCD was employed to investigate the interactive effects of independent factors and get to the more reliable results. The results of study showed that increasing the contact time and GFH dosage improved CFX removal, while increasing initial CFX concentration and pH the had a negative effect on its elimination. The F-value for Lack of Fit and determination coefficient (R^2) were 3.46, 0.0882 and 0.9701, respectively. Also, the CCD selected Quadratic model as the best fitted model for this study. Due to the high removal efficiency of CFX antibiotic with GFH, it is recommended to use this adsorbent for removal of CFX from aqueous solutions.

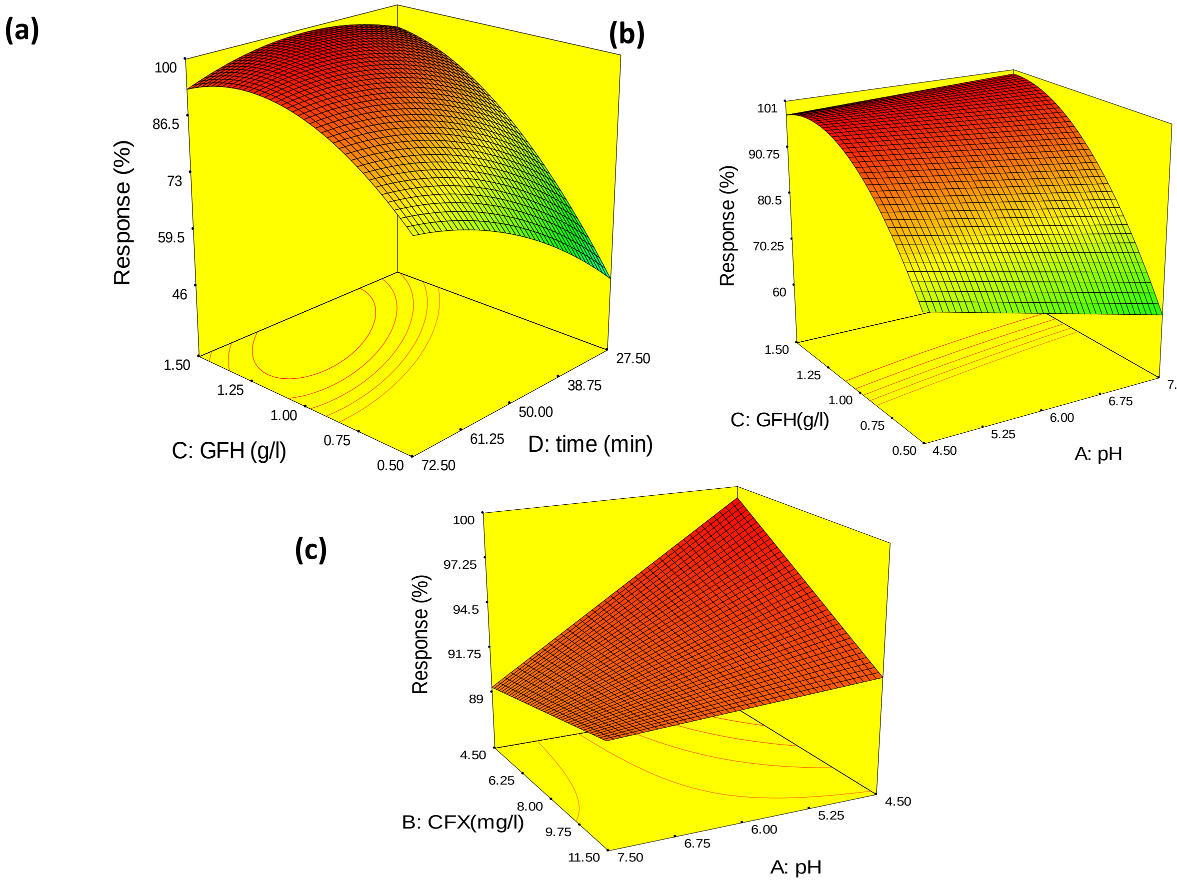

Figure 2: Response surfaces plots for CFX removal as a function of (a) GFH dosage and time (b) GFH dosage and contact time, (c) pH and initial concentration of CFX

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Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

Authors' contribution

All authors of this study have a complete contribution for data collection, data analyses and manuscript writing.

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