Original Article

Cefixime Removal from Aqueous Solutions by Granular Ferric Oxide (GFO): Modeling and Optimization

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Abstract

In recent years, the presence of various pharmaceutical residues such as cefixime (CFX) in aquatic environments has been gaining attention due to its adverse effects on health and ecosystems. Since conventional treatment methods are unable to remove antibiotics, sustainable and efficient approaches are needed to remove these compounds from aquatic environments. In this study, granular ferric oxide (GFO) was used to remove CFX, and the experiments were designed using Design Expert software. The findings were then analyzed using ANOVA test. The results showed that the proposed regression model fit the experimental condition ($R^2 = 0.9701$, $R^2_{adjusted} = 0.9432$, $R^2_{predicted} = 0.83$). Several residual plots were used to confirm the suitability of the model. The initial concentration of 1.84 mg/L, GFO dose of 3.05 mg/L, and contact time of 24.32 minutes were found to be the ideal conditions for CFX adsorption. Moreover, the findings showed that GFO can be effective in absorbing and removing CFX from aqueous environments.

Keywords: Granular ferric oxide, Cefixime, Adsorption, Aqueous solutions

1. Introduction

Recently, the presence of various pharmaceutical residues such as cefixime (CFX) in aquatic environments has been attracting attention due to its adverse effects on health and ecosystems (1). Human excrement, hospital waste, veterinary waste, and pharmaceutical waste are the sources of pharmaceutical compounds entering the environment (2,3). In addition, the efficiency of conventional wastewater treatment to reduce pharmaceutical residues is low; therefore, widespread misuse of drugs, especially antibiotics, causes these compounds to enter the environment (4).

Antibiotics belong to a group of medicines which are used to control bacterial infections (5). Their presence in the environment can increase genotoxicity, antibiotic resistance, and toxicity in the food chain (6). Antibiotic resistance can cause the death of 700 000 people in the world every year (7). CFX is a type of antibiotic from the cephalosporin class. CFX is effective against various bacterial infections. It has been reported that 40% to 50% of the ingested CFX is removed by urination (8,9). In addition, CFX is the most prevalent antibiotic detected in aquatic environments with a maximum concentration of 422.1 ng/L (10).

There are physical (filtration, adsorption, and coagulation/flocculation), chemical (ion exchange and advanced oxidation processes), and biological methods to eliminate or degrade CFX (11,12). The biological treatment cannot effectively degrade antibiotics such as CFX because this process destroys the beneficial

microorganisms involved in biological wastewater treatment (13). Furthermore, membrane and advanced oxidation processes are expensive on a large scale (14). The adsorption process removes CFX from pharmaceutical wastewater more effectively than other physical methods (15). The advantages of the adsorption process include non-toxic residual production, pollutant recovery and reuse, low design cost, suitability for batch and continuous processes, and ease of operation (16). The adsorbent type, pollutant characteristics, and type of wastewater are important parameters affecting the efficiency of the adsorption process (17). In recent years, adsorbents made of organic and inorganic materials have been used to remove various pollutants from aquatic environments (16), including nanocomposite $BiFeO_3$ (18), activated carbon, nanosilica synthesized from rice husk (19), and iron-based adsorbents such as granular ferric hydroxide (GFH) (20) and granular ferric oxide (GFO) (21). Among the advantages of these two adsorbents, mention can be made of high potential removal efficiency (up to 98%), easy operation, low cost, no residue of waste sludge, and simplicity of composition (22).

Response surface methodology (RSM) is a technique employed in the optimization of variables and the interaction between dependent and independent variables. Generally, RSM is adopted for experimental design (23). In previous studies, it has been found that GFO can remove heavy metals from aquatic environments, but research on the removal of organic compounds with this adsorbent is scant. As such, the present study was conducted to investigate the absorption of CFX by GFO with the effect of parameters of initial CFX concentration, dose of GFO, and contact time. Towards this aim, GFO was used and the process was optimized using RSM.

2. Material and Methods
2.1. Preparation of Solutions
The compounds used in this study were all of the analytical grades. The stock solution of CFX (1 g/L) was obtained by adding 0.01 g of CFX powder ($C_{16}H_{15}N_5O_7S_2$ (0.98%), Merck, Germany) to 10 mL of methanol. Then, the as-prepared stock solution was diluted to achieve the necessary concentrations. The fresh stock solution was prepared for each series of runs. A spectrophotometer (Cecil 7250) at a wavelength of 288.5 nm was used to measure CFX. Then, CFX removal efficiency was calculated using equation 1:

$$RE\,(\%) = [(C_i - C_f)/C_i]/100\% \tag{1}$$

Where C_i: initial concentrations, C_f: final concentrations, RE (%): removal efficiency of CFX (%)

2.2. Preparation of GFO
The adsorbent was prepared according to the method used in the study by Tabatabaei et al (21). Electrolysis was utilized to prepare GFO. Iron electrodes were used to produce these granules. After the sediment was formed,

they were rinsed several times with deionized water. Afterwards, it was dried in a furnace at a temperature of 600°C in order to produce ferric oxide.

2.3. Design and Modeling
Central Composite Design (CCD) was used to analyze, estimate, and optimize the efficacy of GFO in the removal of CFX considering three main factors, namely, initial concentration of CFX (mg/L), dose of GFO (mg/L), and contact time (minute). The CCD-based runs conducted by Design Expert software were used as the basis for the experiments. The range of contributions made by the factors and their levels are summarized in Table 1. Additionally, Table 2 displays the matrix of experiments and CCD results.

3. Results and Discussion
3.1. Characterization of GFO
SEM analysis was performed using a HITACHI S-4160

Table 1. Symbol and Code Level of Variables

Variables	Symbol	Code Level				
		-1	-α	0	+α	+1
Initial concentration of CFX (mg/L)	A	1	1.7	2.75	3.79	4.5
Dose of GFO (g/L)	B	0	1.01	2.5	3.98	5
Contact time (min)	C	5	13.1	25	36.89	45

Table 2. Designing Experiments with CCD and Determining the Removal Factors and Efficiency of Each Run

	Experimental Design			Removal Efficiency (%)		
Run	Initial Concentration of CFX (mg/L)	Dose of GFO (g/L)	Contact Time (min)	R%	Predicted	Residual
1	1.7	3.98	36.89	69.6	72.19	2.59
2	2.75	2.5	25	63.16	66.49	3.33
3	2.75	2.5	45	70.7	70.63	-0.07
4	2.75	2.5	25	65.37	66.49	1.12
5	4.5	2.5	25	80.4	82.15	1.75
6	1.7	1.01	13.1	49.1	47.95	-1.15
7	1	2.5	25	85.2	83.83	-1.37
8	2.75	0	25	0	23.31	23.31
9	3.79	1.01	13.1	50.1	46.34	-3.76
10	1.7	1.01	36.89	78.1	77.39	-0.71
11	2.75	2.5	25	70.56	66.49	-4.07
12	2.75	2.5	5	41.6	42.23	0.63
13	3.79	3.98	13.1	69.2	70.07	0.87
14	2.75	5	25	52.2	47.05	-5.15
15	2.75	2.5	25	65.8	66.49	0.69
16	2.75	2.5	25	66.1	66.49	0.39
17	2.75	2.5	25	67.2	66.49	-0.71
18	3.79	1.01	36.89	57.3	54.63	-2.67
19	1.70	3.98	13.1	44	47.30	3.30
20	3.79	3.98	36.89	70.1	70.93	0.83

microscope and a 30 kV acceleration voltage was used to characterize the morphology of GFO. The magnification ranged from 20 to 3000, with a working distance of 5 nm. The GFO image is shown in Fig. 1. Tabatabaei et al (21) presented the FTIR spectra of GFO.

3.2. Model Fitness and Validation

Table 3 presents the results of CCD for CFX adsorption on GFO. Additionally, response graphs were generated by Design Expert. To see how the process factors and responses interacted, the analysis of variance (ANOVA) was used to visually analyze the data. Given the highest R^2 value and complete lack of fit, the CCD selected the quadratic model as the best-fitted model (Table 3). For this investigation, the coefficient of variance was 10.35%. The modified R^2 (0.9432) and the expected R^2 are reasonably in agreement (the difference is less than 0.2). The model is implied to be significant by the model F-value of 36.08. Because of these factors, there is only a 0.01% chance that a significant F-value will occur.

Model terms are considered significant when the *P* value is less than 0.0500. In this model, it was discovered that AB, AC, A^2, B^2, and C^2 had a substantial impact on how CFX absorbed on GFO. The signal-to-noise ratio was measured by Adeq Precision. A signal-to-noise ratio of at least 4 is ideal because it denotes a strong signal. To move around the design space, this model was used. The distribution of data was brought closer to normal distribution by the Box-Cox diagram. The optimal values of Lambda and constant K for this test were determined to be 2 and 0.09, respectively. A quadratic model with regression coefficients is also presented in interaction equation 2.

$$(R_1 + 0.09)^2 = +4420.62 - 82.88A + 496.51B + 952.76C + 705.98AB$$
$$-713.34AC - 178.79BC + 872.24A^2 - 1075.62B^2 - 365.86C^2 \quad (2)$$

3.3. CFX Adsorption and Process Parameters

To determine the effect of variables on CFX removal, perturbation plot and 3D contours were used. Fig. 2 shows the perturbation plot. In the perturbation plot, the sensitivity of each factor in the absorption process is shown
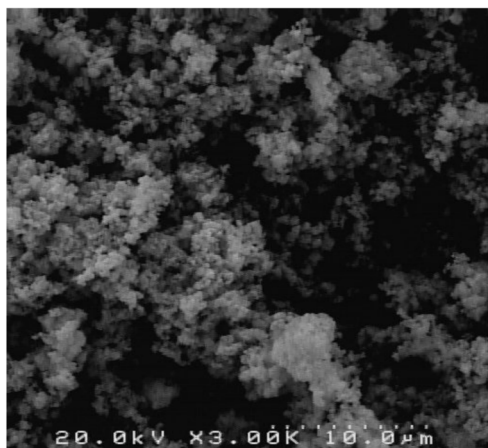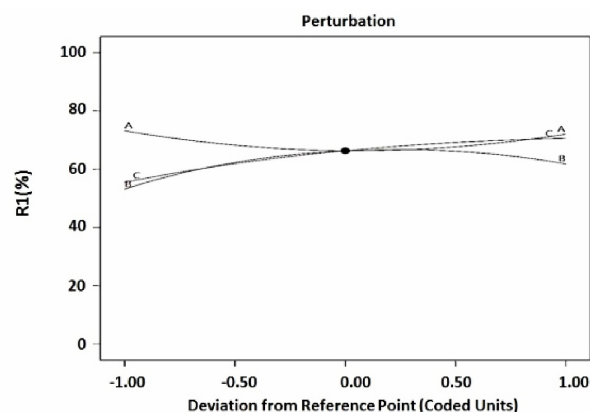

Fig. 1. SEM Images of GFO

Fig. 2. Perturbation Plots for CFX Removal Efficiency (A) Initial Concentration of CFX (B) Dose of GFO (C) Contact Time

Table 3. ANOVA for the CFX Elimination Using GFO Second-order Model

Source	Sum of Squares	df	Mean Square	*F* Value	*P* Value	
Model	5.66E+07	9	6.29E+06	36.08	<0.0001	Significant
A-initial concentration of CFX	93804.33	1	93804.33	0.5384	0.4799	
B-dose of GFO	3.37E+06	1	3.37E+06	19.32	0.0013	
C- contact time	1.24E+07	1	1.24E+07	71.16	<0.0001	
AB	3.99E+06	1	3.99E+06	22.89	0.0007	
AC	4.07E+06	1	4.07E+06	23.37	0.0007	
BC	2.56E+05	1	2.56E+05	1.47	0.2535	
A^2	1.10E+07	1	1.10E+07	62.93	<0.0001	
B^2	1.67E+07	1	1.67E+07	95.7	<0.0001	
C^2	1.93E+06	1	1.93E+06	11.07	0.0077	
Residual	1.74E+06	10	1.74E+05			
Lack of fit	1.20E+06	5	2.40E+05	2.23	0.2002	Not significant
Pure error	5.40E+05	5	1.08E+05			
Cor Total	5.83E+07	19				

$R^2 = 0.9701$, $R^2_{adjusted} = 0.9432$, $R^2_{predicted} = 0.83$, AP = 21.9684, coefficient of variation = 10.35%

by the slope of the lines. Based on this graph, C (contact time) had the highest positive effect on the removal rate.

Figs. 3A and 3B show the interaction of the initial CFX concentration with contact time and initial CFX concentration with adsorbent dose, respectively. Fig. 3A illustrates the effect of interaction between the initial concentration of CFX and the contact time. According to this graph, there is a positive correlation between the amount of pollutant removal and the duration of contact time. Additionally, by increasing the concentration of CFX up to 2.75, the rate of removal of this pollutant decreased, leading to an increase in the rate of removal. The rapid removal of CFX can be attributed to the large number of active sites on the surface of the adsorbent (21). In the study by Kais and Yeddou-Mezenner, the removal of rifampicin increased with increasing contact time at different pH values of the solution (24). Likewise, in the research conducted by Yegane et al, by increasing

the contact time from 0 to 90 minutes, the removal rate of ceftriaxone increased with the help of activated carbon modified with magnetite Fe_3O_4 nanoparticles (25).

As can be observed in Fig. 3B, by increasing the adsorbent dose from 1.01 to 2.5 g/L, the amount of pollutant removal increased. The removal rate increased along with an increase in the initial CFX concentration. In their research, Mostafaloo et al used GFH to remove CFX. They reported the concentration range of CFX and the optimal concentration to be 1-15 mg/L and 8 mg/L, respectively (20). The concentration of CFX in the study by Mostafaloo et al was higher than that in the present study, which explains the reason behind the non-reduction of removal efficiency by increasing CFX concentration due to the fact that the adsorbent capacity had not reached the equilibrium level. Furthermore, the decrease in pollutant removal with increasing adsorbent dose can be attributed to the increase in the level of adsorption relative to a
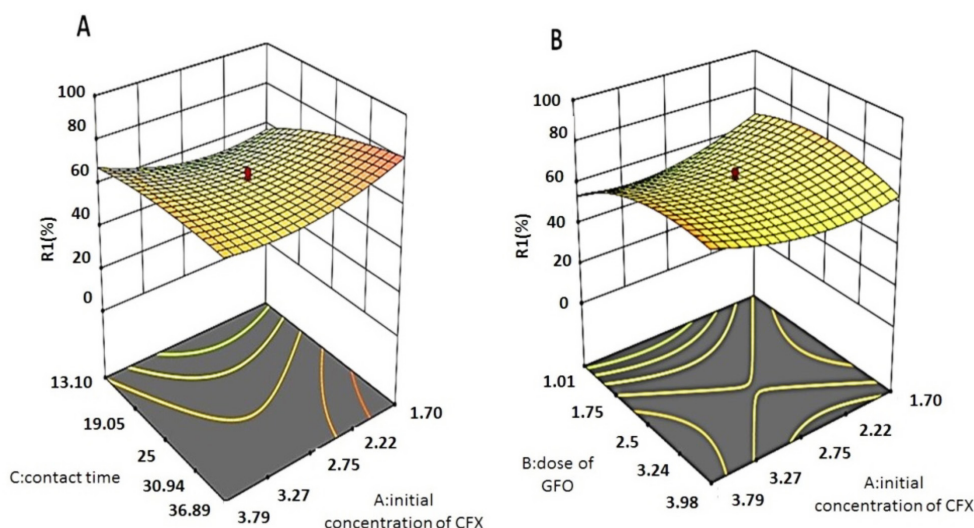

Fig. 3. Response Surface Plots for CFX Removal as a Function of A) Cefixime-Contact time B) Cefixime-adsorbent Dose
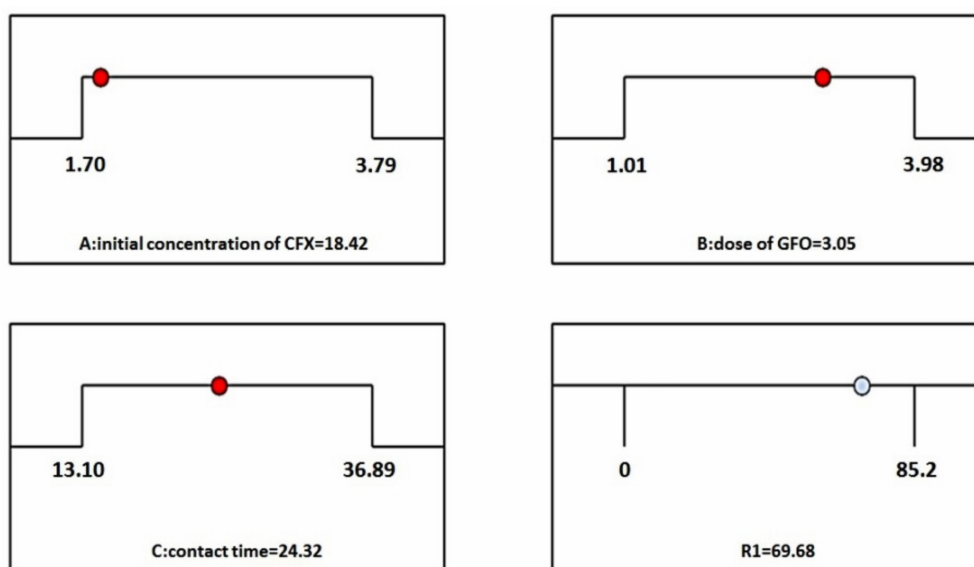

Fig. 4. Desirability Ramp for Optimization of Central Composite with RSM

certain amount. Over time, the adsorption of the pollutant decreases, which is ascribed to the saturation of the active sites in the adsorbent (26). In the study by Moridi et al, increasing the adsorbent dose of Superb nZVI/Copper Slag nanocomposite increased CFX removal (27). Along the same lines, in the research by Hemmat et al, the removal rate of cephalexin increased by increasing the dose of activated carbon (28).

3.4. Optimization
One of the applications of RSM is to determine the optimum conditions. In this research, the optimal predicted removal efficiency (69.68%) was achieved at the initial concentration of 18.42 mg/L, dose of 3.05 g/L, and contact time of 24.32 minutes using the developed model (Fig. 4).

4. Conclusion
In this study, CFX removal was carried out using GFO. RSM was used to save time and expense. The results of the present study showed that GFO can effectively remove CFX from aqueous solution. It is noteworthy that the obtained model for data interpretation was quadratic. The optimal factors obtained for CFX decomposition were as follows: initial concentration of 1.84 mg/L, GFO dose of 3.05 mg/L, and time of 24.32 minutes. In addition, the model used in the study predicted the removal efficiency at the optimal point with a desirability of 68.69. Considering the proper removal of CFX with iron oxide granules, it is recommended that GFO should be used to remove CFX.

Authors' Contribution
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