



Removal of Mefenamic Acid from Aqueous Solution by Fenton Process: Optimization Using Response Surface Methodology with Central Composite Design

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ABSTRACT

In the present study, the three main process parameters in the Fenton process for the removal of pharmaceutical compound Mefenamic acid from an aqueous solution were optimized using response surface methodology (RSM). Central composite design (CCD) was used for process optimization. The primary and secondary interaction effects of the selected parameters such as H_2O_2 , Fe^{2+} and pH on the removal of mefenamic acid were examined. A mathematical model for the removal process based on the selected variables was developed. The interaction effect between the chosen parameters shows that the removal of mefenamic acid was enhanced in the acidic pH range at a high concentration of H_2O_2 and in a medium concentration level of the catalyst Fe^{2+} . The removal efficiency of 81.24% was obtained for mefenamic acid at the optimized condition of variables such as 9.36 mM H_2O_2 , 0.058 mM Fe^{2+} and at a pH value of 2.1.

INTRODUCTION

Pharmaceuticals compounds are one of the emerging contaminants, the presence of which even in trace levels in water sources can cause lethal effects on human beings and aquatic organisms. By the development of modern analytical techniques, various categories of pharmaceutical compounds such as analgesics/anti-inflammatory, β -blockers, psychiatric drugs, antibiotics, lipid regulators, contrast agents, anti-cancer agents, and hormones have been identified in municipal and hospital wastewaters and even in surface and groundwater sources (Wang et al. 2014, Bu et al. 2016). To remove these non-biodegradable and persistent compounds, in addition to the conventional treatment methods, various advanced treatment techniques such as adsorption, reverse osmosis, microfiltration, advanced oxidation, and nano filtration techniques are under research (Rivera-Utrilla et al. 2013).

Among the advanced treatment techniques, advanced oxidation processes (AOPs) are found to be promising. AOPs are based on the formation of highly reactive and non-selective oxidants such as hydroxyl radical ($\bullet OH$), superoxide radical ($\bullet O_2$), hydroperoxyl radicals ($\bullet HO_2$), sulfate radicals ($\bullet SO_4$) and peroxy radical ($\bullet ROO$) generated under atmospheric or subcritical conditions of temperature and pressure, with or

without catalyst and/or energy. These oxidants degrade the persistent organic compounds into carbon dioxide and water or convert them into metabolite forms (Deng & Zhao 2015). There are several types of AOPs based on the techniques used for the in situ formation of oxidant radicals such as chemical, photochemical, sonochemical, microwave-assisted, and electrochemical AOPs (Andreozzi et al. 1999). Fenton process is a chemical AOP method in which $\bullet OH$ radicals are produced by the catalytic decomposition of H_2O_2 by iron salts in an acidic medium (Oturán & Aaron 2014). The advantage of this process is its simple operation principle, environmentally safe nature, short reaction time, and the absence of mass transfer limitation (Naveed et al. 2017). The removal efficiency of the Fenton process depends on various factors such as initial pH, reaction time, initial pollutant concentration, the dosage of Fenton reagent, reagent mole ratio, mode of addition of H_2O_2 , and temperature (Roudi et al. 2018).

Mefenamic acid (MEF) is a nonsteroidal analgesic and anti-inflammatory drug (NSAID). It is commonly used to reduce pain, menstrual pain, dysmenorrhea, migraine and is also used in the treatment of rheumatoid arthritis and other muscular-skeletal diseases (Idrees 2015). In European Union (EU), mefenamic acid is considered a third-class priority pollutant as its concentration in various environmental compartments has been detected larger than the no-effect concen-

tration value of $0.428\mu\text{g.L}^{-1}$ (Chang et al. 2012). The removal of mefenamic acid by photolysis, adsorption on activated carbon, and ozonation showed that 60% removal efficiency in 120 min was achieved by applying a combination of UV and ozone. Also, it reveals that the activated carbon addition did not enhance the removal of the compound (Gimeno et al. 2010). Nitrite-induced photo transformation studies of MEF showed that intermediate photo transformation products are formed and they were found more toxic than mefenamic acid (Chen et al. 2016). Different oxidative processes such as UV, UV/H₂O₂, Fenton, and photo Fenton were investigated and optimized using fractional factorial design and found photo Fenton process using ferric oxalate and hydrogen peroxide at a pH of 6.1 gives a maximum removal of 95.95% in 60 min (Colombo et al. 2016).

Polyurea formaldehyde-Bentonite was tested as an adsorbent for mefenamic acid from water and found maximum adsorption of 16mg.g^{-1} achieved at 47°C at pH 1.5 (Majeed et al. 2017). For practical application of the removal process, it is necessary to optimize the various important factors using experimental design techniques.

The aim of this study is to apply a statistically based technique named the central composite design method to optimize the Fenton process for removal of mefenamic acid from aqueous solutions by varying the selected three main experimental variables such as concentration of oxidant H₂O₂, catalyst Fe²⁺, and pH, and to develop a model to examine the single and combined effect of these variables on the removal process of the compound.

MATERIALS AND METHODS

Materials

Mefenamic acid (C₁₅H₁₅NO₂, 2-[(2,3dimethyl phenyl) amino] benzoic acid, 99%, (Sigma -Aldrich, India), H₂O₂ (30.0% w/v), ferrous sulfate heptahydrate FeSO₄.7H₂O (FS), NaOH, Na₂S₂O₃, and sulphuric acid from Merck (India) were used as such without further purification. All chemicals used were of analytical grade unless indicated otherwise. HPLC grade acetonitrile (ACN), 98% formic acid, and isopropanol (Merck) were used for the analysis.

Experiments

In a typical Fenton experiment, an aqueous solution of mefenamic acid having a concentration of 15 ppm was prepared using Milli Q water and mixed with appropriate concentrations of FeSO₄.7H₂O and H₂O₂ in liquid form in a 250 mL closed pyrex glass reactor. The reactor was placed in a dark chamber to avoid any photochemical reaction. The reaction volume was maintained as 100 mL and stirred continuously

using a magnetic stirrer at 500 RPM. The pH of the sample was maintained by using NaOH and H₂SO₄ solutions as necessary. One drop of 0.1 N sodium sulfite solution was added to each sample taken to quench the action of any excess H₂O₂ present in the sample. All samples taken were filtered through 0.45μm syringe filters before the analysis. The removal of the compound was monitored by analyzing the initial samples and samples taken after 60 min of the interval by using HPLC.

HPLC Analysis

The quantitative determination of mefenamic acid was carried out with an HPLC-UV system on LC2030 plus liquid chromatograph (Shimadzu, Prominence *i*) equipped with a binary solvent gradient pump and an automatic injection system. The compounds were eluted off the C-18 column (250 mm x 4.6 mm packed with 5 μm particle size) with two solvents as mobile phases. The mobile phase consists of solvent A 0.1% formic acid in milliQ water and solvent B 100% acetonitrile. The elution started at 0% B and was then linearly increased to 100% B over 10 minutes at a flow rate of 1.0 mL.min⁻¹ then kept isocratic for 3 minutes and B concentration reached to initial level in the last 2 min. The total run time of the gradient flow method was 15 min. The injection volume was 20 μL and the UV detection wavelength was at 275 nm. The signal acquired from the detector was recorded by Lab Solution software.

Experimental Design

Central Composite Design (CCD)

The CCD was used to optimize the pH, the concentration of H₂O₂ and Fe²⁺ and to evaluate the interaction among these three variables on the removal of Mefenamic acid. CCD is a very efficient design tool for fitting second-order models and optimizing the effective parameters with a minimum number of experimental runs (Bezerra et al. 2008). A CCD consists of cube points made up of design points from a 2^k factorial or 2^(k-1) fractional factorial design with 2k axial or "star" points, and n_c center points (where k is the number of factors) (Im et al. 2012).

In this work, the CCD design consists of 8 cube points (all possible combinations of +1 and -1 for the 3 factors), 5 replicates of central points (coded as 0 for all 3 factors), and 6 axial points (+1.68, -1.68, and 0 for three factors). Thus there is a total of nineteen experiments with three factors coded at five levels.

A regression design is used to mathematically model the response as a function of the independent factors. The following general model equation is used to obtain the optimal response.

$$Y = \beta_0 + \sum_{i=1}^k \beta_i X_i + \sum_{i=1}^k \beta_{ii} X_i^2 + \sum_{i=1}^k \sum_{j=1}^k \beta_{ij} X_i X_j + \epsilon \quad \dots(1)$$

Where Y represents the response variable i.e., the percentage removal of the compound and 'k' is the number of factors, X_i to X_k represents the independent variables, β_i represents the regression coefficients for the linear or primary effect, β_{ii} represents the quadratic coefficients or the squared effect, β_{ij} represent the interaction effect coefficients and ϵ is the random error (Chauhan et al. 2013).

In this study, three independent variables were considered and the quadratic polynomial equation for the response in terms of coded independent variables can be represented as

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 \quad \dots(2)$$

MINITAB 16 was used to obtain the linear, squared, and interaction regression coefficients, and also the response surface and contour plots of the response model.

RESULTS AND DISCUSSION

Preliminary experiments were conducted by univariate method to fix the range of variables and the time interval for the process. The variables X_1 , X_2 and X_3 were the concentration of added H_2O_2 , Fe^{2+} and the pH maintained at the start of

Table 1: Experimental range and levels of selected independent factors.

Independent factors	Range and Levels				
	$-\alpha$	-1	0	1	α
H_2O_2 concentration (mM) (X_1)	2.64	4	6	8	9.36
Fe^{2+} concentration (mM) (X_2)	6.4×10^{-3}	2.0×10^{-2}	4.0×10^{-2}	6.00×10^{-2}	7.36×10^{-2}
pH (X_3)	0.96	3	6	9	11.04

Table 2: CCD matrix in terms of coded units along with the observed and predicted removal values of the compound after 1 hour Fenton process.

Run	Coded variables			% Removal of Mefenamic acid	
	X_1	X_2	X_3	Observed values	Predicted values
1	0.00	-1.68	0.00	27.31	29.38
2	-1.00	-1.00	-1.00	58.65	56.32
3	0.00	0.00	0.00	60.65	60.54
4	1.00	-1.00	-1.00	61.43	59.16
5	-1.00	1.00	-1.00	52.75	51.66
6	-1.00	1.00	1.00	22.70	23.82
7	-1.68	0.00	0.00	36.43	37.09
8	1.68	0.00	0.00	64.50	65.47
9	0.00	0.00	0.00	60.80	60.54
10	0.00	0.00	0.00	60.46	60.54
11	0.00	0.00	1.68	23.41	21.38
12	1.00	1.00	1.00	53.57	54.75
13	-1.00	-1.00	1.00	16.84	17.09
14	0.00	0.00	0.00	60.52	60.54
15	0.00	0.00	-1.68	70.82	74.49
16	1.00	1.00	-1.00	80.16	78.75
17	0.00	0.00	0.00	60.54	60.54
18	1.00	-1.00	1.00	23.85	23.78
19	0.00	1.68	0.00	51.92	51.48

the reaction. The range of variables H_2O_2 (4 - 8 mM), Fe^{2+} (2×10^{-2} - 6×10^{-2} mM), and pH (3 to 9) was fixed based on preliminary studies and the five different levels of each variable were selected based on the central composite design. Table 1 shows the various levels of selected independent factors and Table 2 is the list of coded variables and the observed and predicted removal values of the response.

The model equation obtained for the removal of mefenamic acid in terms of coded variables was as follows:

$$Y = 60.536 + 8.445X_1 + 6.578X_2 - 15.807X_3 - 3.279X_1^2 - 7.123X_2^2 - 4.466X_3^2 + 6.061X_1X_2 + 0.961X_1X_3 + 2.843X_2X_3 \quad \dots(3)$$

Where: Y is the percentage removal of mefenamic acid and X_1 and X_2 were the initial concentration of H_2O_2 and Fe^{2+} in mM and X_3 is the initial pH value.

Statistical Analysis

The quality of the proposed model was checked by the coefficient of determination (R^2) and adjusted R^2 . The coefficient of

determination (R^2) indicates the proportion of variation in the response described by the model. If the value of R^2 is closer to 1, it indicates that the model is good to describe the variation in response as a function of independent variables (Ishak & Malakahmad 2013). Adjusted R^2 is another useful statistical tool to evaluate the model adequacy; it is a modified R^2 value by taking into account the number of covariates or predictors in the model. The 'F value' was the ratio of the mean sum of square due to the model variance and error variance, and is used to test the null hypothesis (Chauhan et al. 2013). The statistical significance was assessed by the lack of fit test. The result of the analysis of variance (ANOVA) was presented in Table 3.

The ANOVA result shows that the linear, quadratic, and interaction terms are significant since the corresponding p-values are <0.05 . A high R^2 value of 0.9936 and an adjusted R^2 value of 0.9873 indicates the significance of the model and its adequacy to predict the response. A normal probability plot of residuals versus response is shown in Fig. 1. The normal probability plot is a graphical method for determining residuals' normality. Fig. 1 shows that the points are close to the straight line and the model is sufficient to describe the response.

Table 3: ANOVA result of the quadratic model for percentage removal of Mefenamic acid.

Source	Sum of squares	Df	Square mean	F value	P value	Remarks
Regression	6238.4	9	693.16	156.08	0.000	Significant
Linear	4972.64	3	1657.55	373.23	0.000	
Square	899.77	3	299.92	67.53	0.000	
Interaction	366.00	3	122.00	27.47	0.000	
Error	39.97	9	4.44			
Lack-of-Fit	39.90	5	7.98			
Pure Error	0.07	4	0.02			
Total	6278.37	18				

$$R^2 = 0.9936, R^2(\text{adjusted}) = 0.9873$$

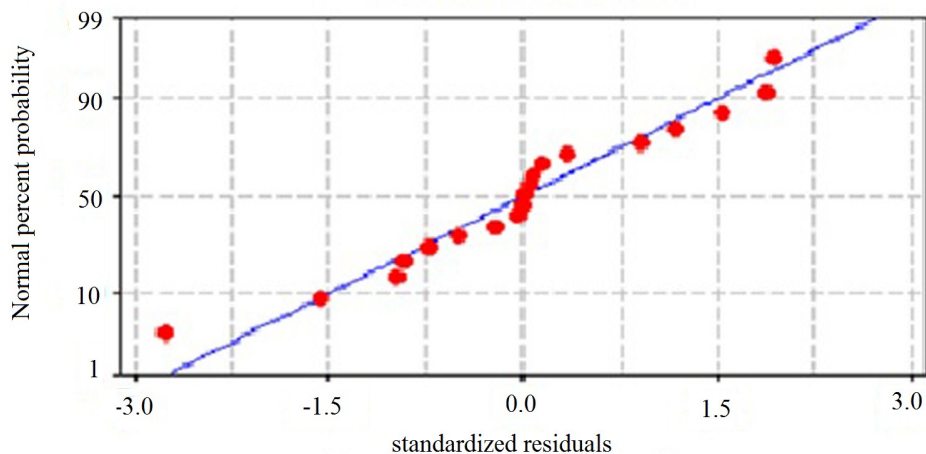


Fig. 1: Normal Probability Plot, % removal of mefenamic acid.

Effect of Independent Variables on the Removal of the Compound

The plot in Fig. 2. shows the effect of independent variables H_2O_2 , Fe^{2+} and pH on the mean removal of mefenamic acid in 19 experiments conducted based on the central composite design. Fig. 2 shows a sharp increase in the average removal value from 4 to 9.36 mM concentration of H_2O_2 . This may be due to the more $\bullet\text{OH}$ radicals produced during the more concentration of H_2O_2 and thus enhancing the removal of the compound (Rezaee et al. 2014). The second curve shows that the mean removal value of mefenamic acid increases up to 55% when the iron concentration changes from 0.0064 to 0.040. Further increase in iron concentration did not show an increase in the removal efficiency. This shows that a high concentration of metal ions was not favoring the removal of this compound. This may be due to the ferrous ion inhibition that occurs at a high concentration of Fe^{2+} in the system. The excess metal ion increases the yield of Fe^{2+} ions which act as a scavenger by quenching the hydroxyl ions formed (Wang et al. 2014). The higher concentration of Fe^{2+} in the system can also result in the production of hydroperoxyl radical ($\bullet\text{HO}$) which has less oxidation potential than hydroxyl radicals (Karale et al. 2014). Effect of pH indicates that the mean removal of mefenamic acid was more favorable at the acidic pH range than at alkaline pH. Mefenamic acid shows more than 50 % average removal efficiency in neutral pH but the removal was less than 30% in alkaline pH.

Combined Effect Among the Independent Variables on the Removal Efficiency

To understand the interaction effect among the independent variable, contour plots and 3D response surface curves

were considered. Fig. 3. shows the profile for the quadratic response surface and the contour plots of % removal of mefenamic acid versus various coded independent variables.

From the contour plot Fig. 3(a), it was evident that more than 70% removal of mefenamic acid was obtained at a higher concentration of added H_2O_2 and Fe^{2+} at a neutral pH range. Fig. 3(b) indicates that a removal value above 60% was obtained at medium concentration levels of H_2O_2 with varying Fe^{2+} concentrations in the acidic pH range of the solution. Interaction between pH and H_2O_2 at medium Fe^{2+} concentration was shown in Fig. 3(c). It shows that removal of mefenamic acid was more than 75% at medium to high levels of H_2O_2 concentration in acidic pH values. This was due to more production of $\bullet\text{OH}$ radicals from added oxidants resulting in the degradation of the compound (Im et al. 2012).

Optimization of Operating Parameters

The optimal value of the independent variable for maximizing the response was obtained by using the Minitab Response optimizer. The value of the process variable obtained corresponding to the optimum response is presented in Table 4. Accordingly, the maximum removal of 82.36% for the mefenamic acid was obtained at optimum conditions of 9.36 mM of H_2O_2 , 0.058 mM Fe^{2+} and at a pH of 2.08. The experimental test was conducted in triplet using the predicted value of independent variables and it shows that the average experimentally observed removal value of 81.24% is very close to the predicted value using the model. It implies that the RSM is a good tool for optimizing the operating parameters in this Fenton process for the removal of mefenamic acid.

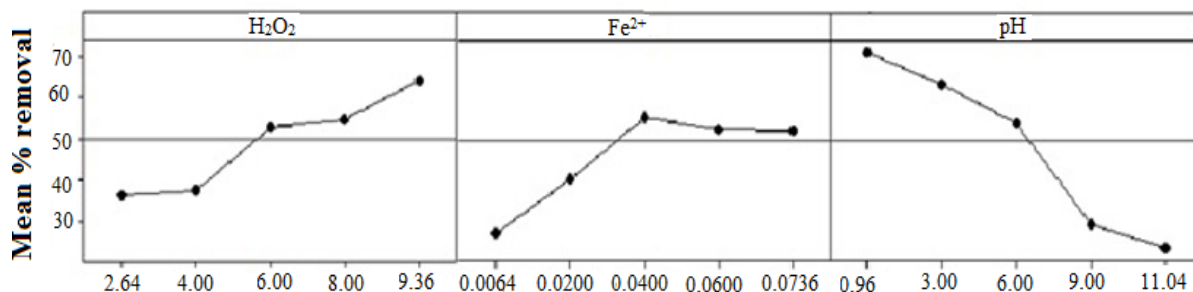


Fig. 2: Primary effect of independent variables H_2O_2 , Fe^{2+} and pH on the removal of mefenamic acid.

Table 4: Optimum value of process variables for maximum removal of Mefenamic acid and its predicted and observed values.

Response	H_2O_2 (mM)	Fe^{2+} (mM)	pH	Predicted Removal (%)	Observed Removal (%)
Removal of Mefenamic acid	9.36	0.058	2.1	82.36	81.24

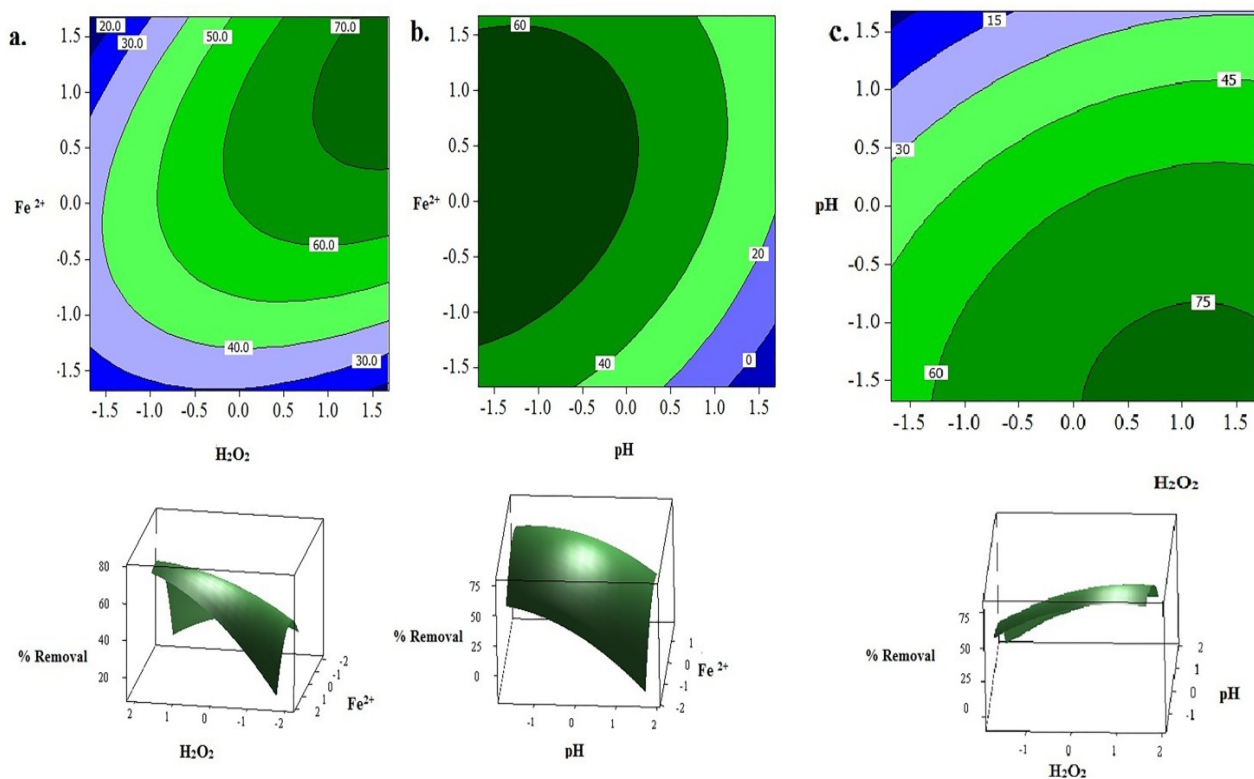


Fig. 3: Contour plots and Response surface plots for mefenamic acid removal versus coded independent variables a) H_2O_2 with Fe^{2+} b) pH with Fe^{2+} and c) H_2O_2 with pH.

CONCLUSION

In this work, RSM was used to optimize the removal of mefenamic acid by using the Fenton process. By using the central composite method, three main operating parameters in the Fenton process including the pH, the initial H_2O_2 and Fe^{2+} concentration were examined. Based on the experimental results and the relationship between the selected independent variables, a quadratic model was obtained. Statistical test by ANOVA showed a high coefficient of determination value ($R^2 = 0.9936$) which indicates a good agreement of the model with experimental data. The interaction effect of experimental parameters on the response was established by response surface curves and contour plots. A high percentage removal value of 82.36% was obtained under the optimal value of variables in the process. Further confirmation experiment under the optimized condition results in a maximum removal value of 81.24%. This indicates that the model is in accordance with the experimental data. Our study implies that RSM based on the central composite method is a useful tool for optimizing the operating parameters for the Fenton removal process of mefenamic acid.

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