Box-Behnken Experimental Design Method Applied to Optimize Photo-Fenton Degradation of Pharmaceutical Atorvastatin Calcium in Aqueous Solution

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ABSTRACT: *Due to the harmful effects on the environment and public health, Atorvastatin calcium (ATO) has to be removed from wastewater using the photo-Fenton process. The novelty of this study is based on the modeling and the optimization of the operating parameters affecting the efficiency of the process by using the Box-Behnken Design (BBD). Operating factors such as pollutant concentration [20-40 mg/L], iron concentration [1-5 mM], and H_2O_2 concentration [5-10 mM] were investigated to evaluate the Chemical Oxygen Demand (COD) abatement.*
A mathematical model of pollutant degradation was established using the MODDE 6.0 software and statistical analysis showed good agreement between experimental results and predictive values with an error of less than 5%, which indicates the soundness of the developed model. The results suggested that the most influential factor on the photo-Fenton degradation of the drug was the initial ATO concentration with an effect of (-22.86), the second was the amount of the H_2O_2 with an effect of (+2.82), the third was the concentration of Fe^{3+} ions with an effect of (-2.79). The model obtained by BBD corresponding to the best value of the COD abatement rate (100%) of ATO led to the following optimal conditions: initial concentration of pollutant equal to 20 mg/L, a catalyst concentration equal to 1 mM and a concentration of hydrogen peroxide equal to 10 mM.

KEYWORDS: *Atorvastatin calcium; Box-Behnken; Degradation; Experimental design; Photo-Fenton.*

INTRODUCTION

Water is an essential component of life. Due to the contamination of the water sources with organic chemicals such as pharmaceutical compounds the quality of life decreased and a very serious problem appeared.

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The development of the pharmaceutical industry combined with strong population growth, supports the degradation of the quality of surface, and groundwater has an impact on the natural environment, human health, and the balance of ecosystems [1,2]. Amongst a variety of medicines used, we can find Atorvastatin (ATO) which belongs to the statins: a group of pharmaceuticals used for lowering cholesterol levels in the blood and also applied for the reduction of cardiovascular-related morbidity and mortality in patients with or at risk of coronary heart diseases [3]. More than 80 pharmaceutical products were detected in several countries in urban wastewater at concentrations varying from ng/L to µg/L [4,5], Atorvastatin was widely detected in surface and effluent water [6,7], it was quantified at concentrations ranging from 42 to 209 ng/L, [8,9]. The important side effects of atorvastatin are myopathy [10], rhabdomyolysis [11], increased concentrations of liver enzymes, muscle problems, diabetes [12,13], cognitive loss, neuropathy, pancreatic, hepatic, and sexual dysfunctions [14]. Moreover, various studies have shown that the presence of antibiotics and their transformation products, even in low concentrations, could lead to the disruption of life cycles, critical for aquatic ecology, and animal and plant production [15-17].

In this sense, it is imperative to develop an effective treatment technique for drug removal and their intermediates in wastewater. Conventional methods of pharmaceutical substance removal include biological methods [18], coagulation-flocculation [19], ultrafiltration membranes [20], adsorption [21, 22], and Photocatalytic Process [23] have been tested but it is important to comment here that despite of atorvastatin pollution in diverse water resources only activated carbon as sorbent and synthesis composite is described for the removal of atorvastatin in water [24, 25], furthermore, it was observed that those methods are either expensive or do not often reach the threshold set up by the water standards.

During the last decade, a lot of research has focused on a new class of oxidation techniques: Advanced Oxidation Processes (AOPs) appear to be powerful processes for treating wastewater and surface water contaminated with pharmaceutical compounds [26]. They are based on oxidative reactions mediated by the hydroxyl radical ($^{\bullet}OH$), a powerful species non-selective source of oxidation with a high reduction potential (E_o = 2.73V versus the normal hydrogen electrode) [27]. These technologies have already shown their potential in the treatment of toxic and "biologically recalcitrant" organic pollutants [28-30]. A combination of hydrogen peroxide and UV radiation with Fe (II), the so-called photo-Fenton which is an environmentally friendly process, a non-selective de-pollution technique that only requires a supply of low concentration iron as a catalyst and hydrogen peroxide (H_2O_2), the reagents used are safe to handle and non-threatening to the environment (i.e., H_2O_2 used does not load in the system and is decomposed to harmless substances, whereas only analytical amount of Fe-ion can be used), produces more hydroxyl radicals in comparison to the conventional Fenton method or the photolysis and required alow-cost equipment, thus promoting the degradation of organic pollutants [31]. UV light leads not only to the formation of additional hydroxyl radicals but also to the recycling of ferrous catalysts by reduction of Fe^{3+}. In this way, the concentration of Fe^{2+} is increased and the overall reaction is accelerated. A simplified mechanism of the photo-Fenton process can be described as follows:

$$Fe^{3+} + H_2O \rightarrow Fe\,(OH)^{2+} + H^+ \tag{1}$$

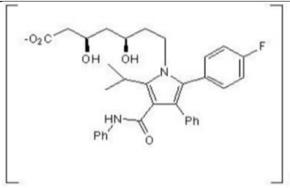
$$Fe\,(OH)^{2+} + h\nu \rightarrow Fe^{2+} + HO^{\bullet} \tag{2}$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe\,(OH)^{2+} + HO^{\bullet} \tag{3}$$

The heterogeneous photo-Fenton reaction can solve the problem of eliminating and re-using Fe^{3+} from the reaction system at the end of the process using magnets [32]. The photo-Fenton process is particularly attractive for the degradation of highly toxic and/or non-biodegradable compounds due to the abundance and non-toxicity of iron [33], it frequently leads to complete mineralization of organic pollutants into CO_2 and H_2O [34].

Parameters optimization is one of the most important stages in the process of development with economic impact. Interactions between independent variables are not considered in the traditional optimization method «one-factor-at-a-time approach», in addition, the latter takes a long time [35]. To deal with this problem, Response Surface Methodology (RSM) is an effective optimization tool used in fewer experimental trials to identify many factors and their interactions [36, 37], Box-Behnken Design (BBD) is amongst the most designs commonly used in various experiments, where it needs smaller test numbers compared to all the RSM [38]. It is useful in avoiding experiments performed under extreme conditions, for which unsatisfactory results might occur [39], used to examine

Table 1: ATO characteristics

Name of compound	Atorvastatin calcium
Abbreviation	ATO
Molecular formula	$(C_{33}H_{34}FN_2O_5)_2Ca$
Molar mass (g/mol)	558.64
pKa	pK_a= 4.5 [41]
Solubility in distilled water	140.9 mg/L [42]
Chemical structure	

the relationship between response variables and optimize the individual and interaction effects of various variables [40]. The novelty of the study is based on the modeling and the optimization of the operating parameters affecting the efficiency of the photo-Fenton process for removing organic compounds and recalcitrant pollutants from wastewater by using the Box-Behnken design, which remains scarcely investigated in this research area. This work deals with the degradation of ATO in an aqueous solution by using the photo-Fenton process. The influence of the initial ATO concentration (x_1), the initial concentration of Fe^{3+} ions (x_2), and the initial concentration of H_2O_2 (x_3) on COD abatement was statistically investigated by experimental design in a batch reactor. The model equation obtained by the BBD was used to determine the optimal values of the operating parameters.

EXPERIMENTAL SECTION

Reagents

The pharmaceutical product used as an organic pollutant model is Atorvastatin calcium (Sigma Aldrich, 99%), its characteristics are summarized in Table 1.

H_2SO_4 (Sigma Aldrich, 95-97%), $FeSO_4.\ 7H_2O$ (Fluka Guarantee, 98%), H_2O_2 (Scharlau, 33%) and Na_2CO_3 (Sigma Aldrich, 99.5-100%) were of analytical quality and the solutions were prepared with distilled water.

Experimental

Degradation of ATO by the photo-Fenton process was carried out in a batch double-jacketed glass reactor under UV PHILPS PL-L 24W / 10 / 4P U.V lamps with a maximum emission of 365 nm (Fig. 1). The lamp irradiance (45 W/m^2) received by the drug solution was determined by using a DALE40 Phototherapy Radiometer, contained in a quartz tube immersed in the reaction liquid. According to *Sarrai et al.*, for higher pH values, low activity is detected because of the decrease of free iron species due to ferric oxyhydroxide precipitation, formation of different complex species, and breakdown of H_2O_2 to O_2 and H_2O. Low activity at pH values, more acidic than the optimal level, results from Fe (III) forming different complex species in solution [43], and also acidic medium prevents the precipitation of iron [44, 45]. For this reason, the solution pH is adjusted to 3 with sulfuric acid (0.1M) and continuously stirred (500 rpm) to ensure homogeneity of the solution at room temperature (25°C). The reactor is covered before the lamp is switched on, so as not to have an additional source of sunlight and to protect our eyes because UV rays are dangerous. After 2h of treatment, the sample was centrifuged, and the supernatant neutralized with Sodium Bicarbonate (2 g/L) and heated in a water bath at 90°C for 2 to 3 minutes to remove left-over H_2O_2 from the samples before estimating their COD [46]. The residual COD was analyzed by AQUALYTIC AL 200 COD Vario using potassium dichromate in a hot and acidic medium by METHOD 410.4 Edited by James W. O'Dell [47].

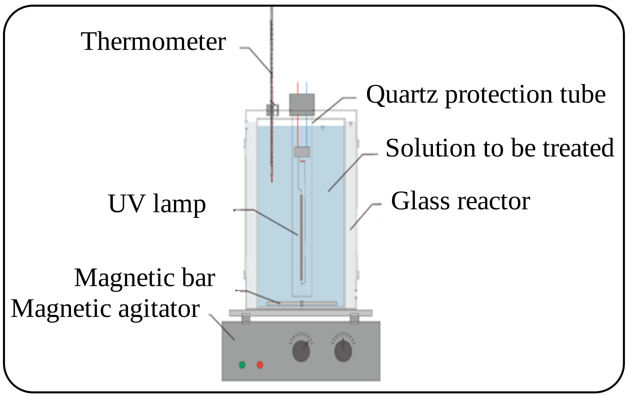


Fig. 1: Experimental setup

The COD abatement rate was calculated by the Eq. (4):

$$\mathrm{Re}\ (\%) = \frac{COD_0 - COD}{COD_0} \times 100 \qquad (4)$$

Were COD_0 and COD are the initial and the residual COD (mgO_2/L)

The optimization of different operating parameters (pollutant concentration, Iron concentration, and H_2O_2 concentration) giving the best COD abatement has been performed using the Box-Behnken experimental design.

Table 2: Values and levels of the operating parameters.

Key	Factors	Level -1	Level 0	Level +1
x_1	[ATO] (mg/L)	20	30	40
x_2	$[Fe^{3+}]$ (mM)	1	3	5
x_3	$[H_2O_2]$ (mM)	5	7.5	10

Fig. 2: Effect of main factors and interactions.

Box-Behnken design

Box-Behnken Design (BBD) among the second-order RSM designs requires little experience to optimize a three factors process; it is presented on cubes where the experimental points are placed in the middle of the edges, and points are then added to the center of the study area.

The number of experiments to perform for a Box-Behnken experimental design was calculated by the following equation [48, 49]:

$$N = 2 \times K(K-1) + \theta \tag{5}$$

Where: K is the number of factors and θ is the number of points in the center.

The number of tests (N) required to construct the three-factor Box-Behnken matrix meaning is 15 (K= 3 and θ=3).

The pollutant concentration (x_1), Iron concentration (x_2), and H_2O_2 concentration (x_3) were chosen as the most influential study factors on the photo-Fenton degradation of ATO. The experimental BBD levels selected for each factor used in this study are presented in Table 2.

All other parameters of the reaction such as: pH of the solution (~ 3), lamp intensity (45 W/m^2), ambient temperature (~ 25 °C), stirred speed (500 rpm), time (2 hours) and volume of the solution (1L) have been fixed during the experiments. The COD abatement rate calculated by Eq. (1) was chosen as the response in these experiments.

RESULTS AND DISCUSSIONS

The matrix of experiments and the experimental results (responses) obtained during the realization of the 15 tests of the Box-Behnken plan are presented in Table 3.

Table 3: Experimental design and results of ATO degradation.

Test N°	[ATO] (x_1)	$[Fe^{3+}]$ (x_2)	$[H_2O_2]$ (x_3)	COD_{Obs} (%)	COD_{Pred} (%)	Error (%) (Obs–Pred)
1	-1	-1	0	90.71	92.297	-1.588
2	+1	-1	0	30.50	30.925	-0.425
3	-1	+1	0	71.50	71.075	0.425
4	+1	+1	0	42.57	40.983	1.587
5	-1	0	-1	76.53	74.189	2.341
6	+1	0	-1	44.76	43.581	1.179
7	-1	0	+1	93.77	94.949	-1.179
8	+1	0	+1	31.75	34.091	-2.341
9	0	-1	-1	48.85	49.604	-0.754
10	0	+1	-1	55.07	57.836	-2.766
11	0	-1	+1	71.82	69.054	2.766
12	0	+1	+1	50.41	49.6563	0.754
13	0	0	0	64.74	62.2	2.540
14	0	0	0	61.53	62.2	-0.670
15	0	0	0	60.33	62.2	-1.870

To interpret the results, MODDE 6.0 software was used to calculate the model coefficients and the corresponding standard deviations. Analysis of variance was performed to adapt the response functions (COD abatement rates) to the experimental data. The second-order model obtained according to a BBD was given in Eq. (6).

$$Y(\%) = 62.2 - 22.86x_1 - 2.79x_2 + 2.82x_3 + 7.82x_1x_2 - 7.56x_1x_3 - 6.91x_2x_3 + 0.89x_1^2 - 4.427x_2^2 - 1.39x_3^2 \tag{6}$$

The main effects and interactions shown in Fig. 2, demonstrate that drug concentration and Iron concentration had a negative effect, the COD abatement increases with the decrease of initial drug concentration and Iron concentration. Contrary, H_2O_2 concentration had a positive effect on the COD abatement.

At higher iron concentrations, the excess of Fe^{2+} ions act as hydroxyl radical scavengers, it competes with the ATO molecules for the hydroxyl radicals, which reduces the hydroxyl radicals in the solution and therefore the degradation rate also decreases [50].

$$Fe^{2+} + OH^{\bullet} \rightarrow Fe^{3+} + OH^{-} \tag{7}$$

As for the H_2O_2 concentration, its rise generates a higher number of hydroxyl radicals and consequently promotes the degradation of the pollutant.

The interaction between ATO concentration/drug concentration and ATO concentration / Iron concentration has a positive effect on COD abatement. However, the interaction of Iron concentration/Iron concentration, H_2O_2 concentration / H_2O_2 concentration, ATO concentration / H_2O_2 concentration, and Iron concentration/H_2O_2 concentration hurts the degradation performance.

Table 4: Statistical analysis of the results

Statistical analysis	R^2	R^2 adjusted	Q^2	Reproducibility	$SS_{regression}$	$SS_{residue}$
Values	0.991	0.975	0.884	0.9997	5050.85	45.98

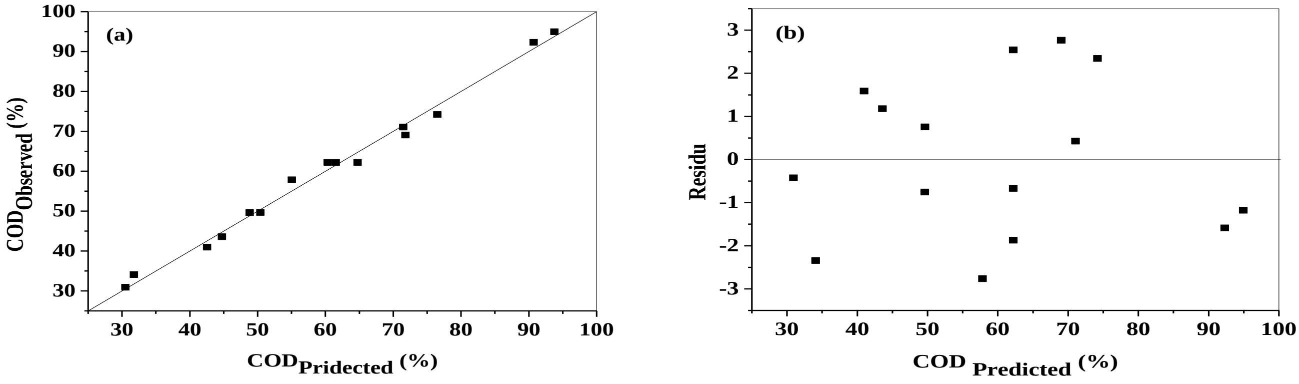


Fig. 3: Observed responses based on predicted responses and the scatter plot.

Evaluation of the statistical models

From the results shown in Table 4, the coefficient of determination (R^2~ 1) and the prediction coefficient (Q^2> 0.8) indicate that the model shows the best fit and has a good prediction [51].

The adequacy of the model was confirmed by the R^2 adjusted values which were close to the corresponding values R^2. On the other hand, the values of the average square regression ($SS_{regression}$) which were greater than the mean square of the residues ($SS_{residus}$) indicated the adjustment of the model (Table 4) [52]. The predicted values were close to the observed values (Fig. 3a), with R^2 equal to 0.991, which was the most important assumption for the verification of the statistical model. Also, the residue dispersion diagram (Fig. 3b) shows that the model was well validated; this validity returns to the random representation of the points.

Simplification of the model

To compare the influence of the coefficients, the significance of each model parameter was determined by p-value, the smaller p-value corresponding to a more significant coefficient. If the "p-value" is less than 0.05, the coefficient is considered statistically influential. But, if the "p-value" is close to or greater than 0.05 the coefficient is not influential [53, 54]. According to the results shown in Table 5, the pollutant concentration (x_1) was highly significant because the p-value was much smaller than 0.05.

The coefficients that p-values were greater than 0.05 (Table 5) must be eliminated; the Eq. (6) was simplified as Eq. (8):

Table 5: P-value of the model coefficients.

	P-value	Remark
a_0	3.32E-7	Significant
a_1	4.20E-6	Significant
a_2	0.048	Significant
a_3	0.046	Significant
a_{12}	0.0036	Significant
a_{13}	0.0041	Significant
a_{23}	0.0061	Significant
a_{11}	0.5961	Not Significant
a_{22}	0.0424	Significant
a_{33}	0.4187	Not Significant

$$Y(\%) = 62.2 - 22.86x_1 - 2.79x_2 + 2.82x_3 + 7.82x_1x_2 - 7.56x_1x_3 - 6.91x_2x_3 - 4.27x_2^2 \quad (8)$$

According to the equation (Eq. (8)), the initial ATO concentration (x_1) has the strongest effect on the response with a negative effect (b_1 = -22.86), the negative sign of the b_1 coefficient suggests that the removal yield of ATO decreased with increasing initial ATO concentration. The results obtained indicate that the degradation efficiency of ATO was inversely proportional to its initial concentration; this may be attributed to a competitive consumption of the hydroxyl radicals between the ATO molecules and the generated by-products.

The second in the order was the amount of H_2O_2 with a positive effect (b_3 = +2.82). These results are in good agreement with the literature where it has been shown that increasing the concentration of hydrogen peroxide improves the efficiency of the photo-Fenton process.

Table 6: Test points for model validation.

Test	x_1	x_2	x_3	COD (%)		
				Obs	Pred	Obs-Pred
16	+0.5	+0.5	+0.5	27.47	26.89	0.58
17	-0.5	-0.5	-0.5	39.06	37.23	1.83
18	-0.5	-0.5	+0.5	38.99	36.29	2.7
19	+0.5	+0.5	-0.5	28.56	27.82	0.74

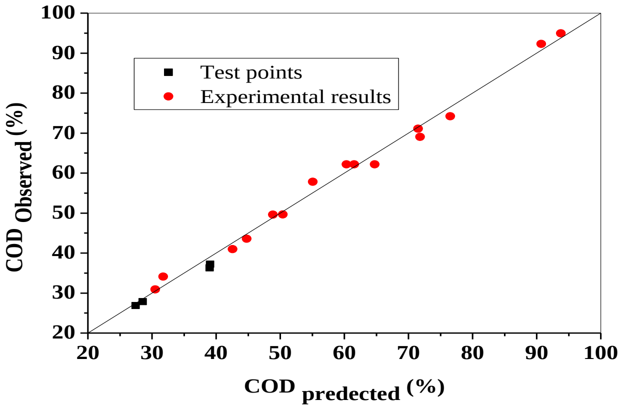


Fig. 4: Adjustment of the test points with the experimental values.

The third was the concentration of Fe^{3+} ions with a negative effect (b_2 = - 2.79). This decrease in degradation efficiency of ATO for increasing concentrations of Fe^{3+} might be due to the increase in brown turbidity which interferes with the absorption of light necessary for the photo-Fenton process and to the scavenging effects of hydroxyl radicals by Fe^{3+} and Fe^{2+} as these parasitic reactions become competitive at higher concentrations of Fe^{2+} or Fe^{3+} according to the Eq. (9) and Eq. (10).

$$Fe^{2+} + HO^{\bullet} \rightarrow Fe^{3+} + OH^- \qquad (9)$$

$$Fe^{3+} + {}^{\bullet}HO_2 \rightarrow Fe^{2+} + O_2 + H^+ \qquad (10)$$

After the simplification of the model, its validation was necessary, for that, R^2, adjusted R^2 and the test points were used to estimate their adequacy.

A good adjustment of Eq. (8) to the experimental data was checked through the high correlation coefficient values obtained of R^2= 0.989 and $R^2_{adjusted}$=0.978.

The comparison between predicted and observed responses for the test points (Table 6) and the good adjustment of the test points with the experimental values (Fig. 4) shows that the simplified model was validated.

The optimal conditions corresponding to the best values of the COD abatement at various ATO concentrations were summarized in Table 7.

Table 7: Optimal values of COD abatement.

[ATO] (mg/L)	$[Fe^{3+}]$ (mM)	$[H_2O_2]$ (mM)	COD (%)
20	1	10	100
30	1	10	69.05
40	5	5	51.24

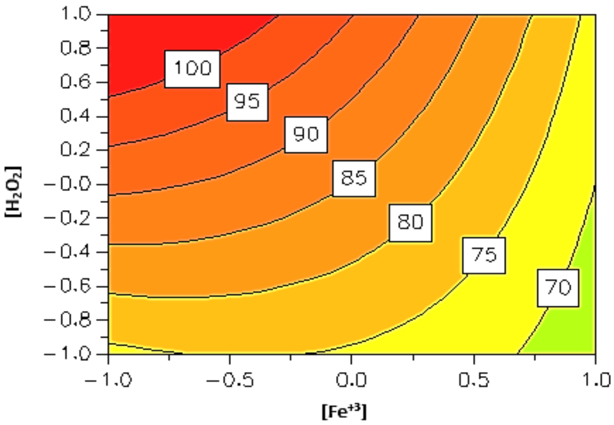


Fig. 5: Contour plots showing the effect of H_2O_2 concentration (x_3) and Fe^{+3} concentration (x_2) on the yield of COD abatement, x_1: $[ATO]_0$ = 20 mg/L, time 2h, T =25°C.

Contour plots analysis

After assessing the adequacy of the models, MODDE 6.0 software was further used to obtain the contour plots to have the conditions of the best yield of COD abatement. Only the curves given the best yield were represented.

Analysis of Fig. 5 indicated that the optimal conditions found for the photo-Fenton degradation were: $1 \leq [Fe^{+3}] \leq 2.38$ mM and $8.807 \leq [H_2O_2] \leq 10$ mM for $[ATO]_0 = 20$ mg/L. Under these conditions, the obtained COD abatement yield was 100 %.

According to the Fig. 6, the COD abatement yield was obtained under the following optimal conditions by using the photo-Fenton process: $20 \leq [ATO] \leq 22.2$ mg/L, $5 \leq [H_2O_2] \leq 8.827$ mM, $[Fe^{+3}]_0$ =5 mM.

Contour plots (Fig. 7) analysis led to the following optimal conditions for the COD abatement: $20 \leq [ATO] \leq 22.2$ mg/L, $1 \leq [Fe^{+3}] \leq 2.406$ mM, in these conditions, the COD abatement was 100 %.

Some studies have shown that at higher catalyst doses, COD removal decreases because catalyst dosage will limit the further acceleration of the reaction rate, which leads to the generation of electron-hole effect to generate superoxide radicals with weaker oxidation capacity than that of •OH and reduces the catalytic performance of the reaction system [55, 56].

Table 8: Comparison of the photo-Fenton process to other wastewater treatment technologies for ATO removal.

Removal efficiency (%)	Reaction time (min)	Analysis ethods	Treatment methods	ATO Concentration	References
23	160 min	UV visible	Photochemical degradation	20 mg/L	[58]
90	3 h	HPLC	Adsorption	1 mg/L	[60]
77.1	60 min	UV visible	Electrocoagulation	5 mg/L	[61]
21	1h	UV visible	Photocatalysis TiO_2	20 mg/L	[62]
100	2 h	DCO	Photo-Fenton	20-40 mg/L	Present study

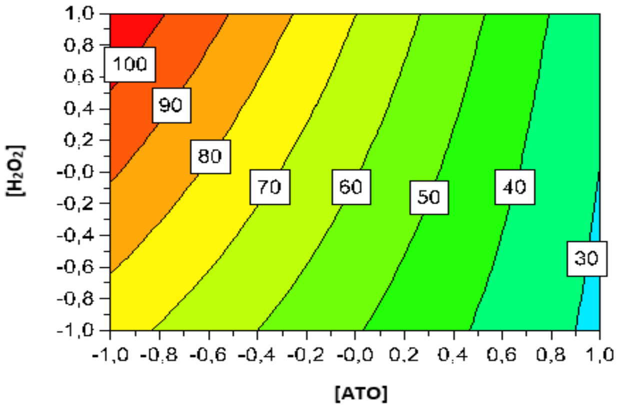


Fig. 6: Contour plots showing the effect of H_2O_2 concentration (x_3) and ATO concentration (x_1) on the yield of COD abatement, x_2: $[Fe^{+3}]_0$ = 1 mM, time 2h, T=25°C.

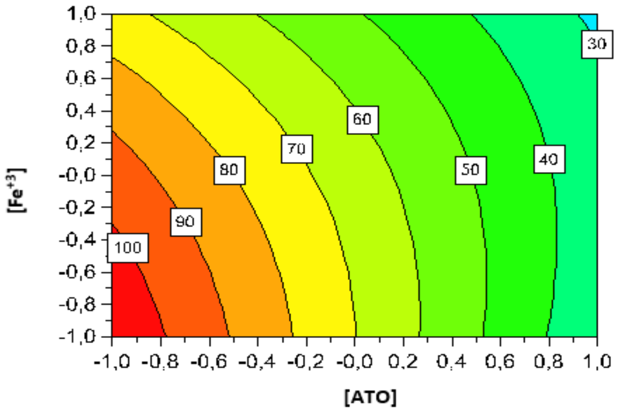


Fig. 7: Contour plots showing the effect of ATO concentration (x_1) and Fe^{+3} concentration (x_2) on the yield of COD abatement, x_3: $[H_2O_2]0$ = 10 mM, time 2h, T=25°C.

The decrease in COD removal with an increase in ATO concentration may be explained by the fact that when at low ATO concentration the hydroxyl radical is trapped by hydrogen peroxide, however, this trapping becomes negligible at high ATO concentration [57]

On the other hand, the higher concentration of H_2O_2 can increase COD abatement, it is due to the production of $^\bullet OH$ which is the major cause of AOT degradation. However, excess of H_2O_2 concentration may promote an inhibitory effect by the hydroxyl radicals scavenging and the formation of another radical ($^\bullet HO_2$) (Eqs. (11)-(15)), which has an oxidation potential considerably smaller than $^\bullet OH$ [55-59].

$$H_2O_2 + {}^\bullet OH \rightarrow H_2O + {}^\bullet HO_2 \quad (11)$$

$${}^\bullet OH + {}^\bullet OH \rightarrow H_2O_2 \quad (12)$$

$${}^\bullet HO_2 + H_2O_2 \rightarrow {}^\bullet OH + H_2O + O_2 \quad (13)$$

$$2{}^\bullet HO_2 \rightarrow 2H_2O_2 + O_2 \quad (14)$$

$${}^\bullet HO_2 + {}^\bullet OH \rightarrow H_2O + O_2 \quad (15)$$

Comparative review

The ATO removal efficiency by the photo-Fenton process was compared with other water treatment technologies (Table 8). The relevance of the photo-Fenton process to the removal of ATO was confirmed since the observed removal yields were similar to or greater than those reported in other findings.

CONCLUSIONS

The objective of this work is to study the performance of an advanced "photo-Fenton" oxidation process on the degradation of Atorvastatin in an aqueous medium and the modeling of the process by a mathematical equation. The application of the Box-Behnken plan for three factors, allowed us to establish a very representative model of the degradation. This model has been validated by analytical method, which indicates that the model is highly significant and in good agreement with the experimental results. The initial ATO concentration (x_1) has the strongest effect on the response with a negative effect (b_1 = -22.86), the negative sign of the b_1 coefficient suggests that the removal yield of ATO decreased with increasing initial ATO concentration. The second in the order was the amount of H_2O_2 with a positive effect (b_3 = +2.82). The third was the concentration of Fe^{3+} ions with a negative effect (b_2 = - 2.79).

The results obtained show that Atorvastatin is completely degraded by photo-Fenton under the optimal conditions: pollutant concentration (x_1): 20 mg/L, iron concentration (x_2): 1 mM, and H_2O_2 concentration (x_3): 10 mM. The iso-response curves highlight the existence of these optimal conditions. Finally, the ATO removal efficiency by the photo-Fenton process was compared with other water treatment technologies, the comparison indicates that the proposed approach based on the photo-Fenton process would be an alternative to degrade ATO in aqueous solutions. Also, RSM has been proven as a reliable statistical tool in studying chemical treatment processes to achieve an optimal response with a minimum number of experiments.

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