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Mineralization of Hydrochlorothiazide using Hydrogen Peroxide in Subcritical Water

Erdal Yabalak[1]*, Özkan Görmez[1], Yahya Nural[2]*

[1]University of Mersin, Faculty of Arts and Science, Department of Chemistry, TR-33343, Mersin, Turkey.
[2]University of Mersin, Faculty of Pharmacy, Department of Analytical Chemistry, TR-33169, Mersin, Turkey.

Abstract: In this paper, we investigated the mineralization of hydrochlorothiazide, a diuretic drug which is used for the treatment of hypertension, using H_2O_2 as the oxidizing agent in subcritical water as a medium. Response surface methodology was applied to optimize experimental parameters such as temperature, treatment time, and concentration of the oxidizing agent. The highest TOC removal was obtained as 85.22% in 147.3 minutes of treatment time at 403 K using 80 mM of hydrogen peroxide. The reliability of the performed method was evaluated by ANOVA and the theoretical equation of TOC removal of hydrochlorothiazide was proposed. *F* and *p* values of the model were determined as 62.88 and lower than 0.0001, respectively.

Keywords: Hydrochlorothiazide, Degradation, Subcritical water, Hydrogen peroxide, Response surface methodology.

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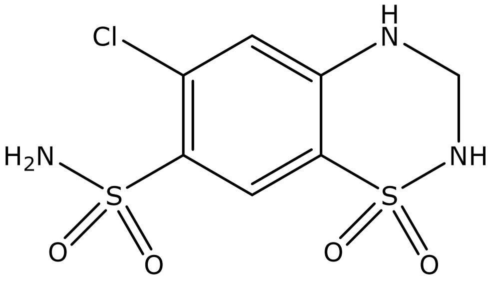
***Corresponding authors.** E-mail: Erdal Yabalak: yabalakerdal@gmail.com and
Yahya Nural: ynural1805@yahoo.com.

INTRODUCTION

Pharmaceuticals are released to the environment during the production, storage, and post-consumption phases. Their damage to the environment, hence their damage to living systems, may be restrained by considering their environmental fate. For this reason, a large number of studies have been carried out on identification of degradation product of the pharmaceuticals and how to release them to the environment in a harmless manner (1-5). In this context, it is known that many methods have been developed to convert pharmaceuticals into harmless or less harmful species, thus safely releasing them into the environment. One of these methods is degradation of the pharmaceuticals using various chemicals in a variety of media (2). Yabalak *et al*. (6-9) have used hydrogen peroxide in subcritical water medium for degradation of various drugs such as propham, ticarcillin, paracetamol and oxacillin. Turabik *et al.* (10), have performed oxidative degradation of imidacloprid by electrochemical advanced oxidation. Hasan *et al* (11), have carried out degradation of sulfisoxazole on pure TiO_2 under visible light irradiation. Furthermore, Giahi (12) has carried out photodegradation of diclofenac sodium by addition of a small amount of $K_2S_2O_8$ in the medium and Ji *et al.* (13) have carried out degradation of sulfaquinoxaline by a ferrous ion-activated peroxymonosulfate oxidation process.

Hydrochlorothiazide (abbreviated as HCT, 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, Figure 1) belongs to the class of thiazides and is mainly used as a diuretic as well as for the treatment of hypertension, and symptomatic edema (14, 15). However, it is reported that HCT is one the most ubiquitous contaminants in the sewage and river waters in some countries (16) such as Serbia (17) and Spain (4). There are various studies in the literature related to the degradation of HCT using different methods. Real *et al.* (18) have reported the degradation of HCT in different media via oxidation by means of UV radiation, Fenton's reagent and ozone. Mahajan *et al.* (19) have performed the degradation of HCT under hydrolytic, oxidative, photolytic and thermal stress conditions, and have characterized its degradation products using high performance liquid chromatography. In another study, Márquez *et al.* (20) have carried out the degradation of HCT and some other drugs in ultrapure water and in water from a municipal wastewater treatment plant, by various oxidation methods such as conventional ozonation, photolytic ozonation, TiO_2 catalytic ozonation, *etc*. Contreras *et al.* (21) have reported the degradation of HCT via electrochemical oxidation. Moreover, there are several other studies in the literature for the degradation of HCT using similar degradation methods (22-25). However, to the best of our knowledge, there is not any study related to the degradation of HCT using hydrogen peroxide in subcritical water medium.



$C_7H_8ClN_3O_4S_2$

Figure 1: Chemical structure of HCT.

Subcritical water is defined as water which is heated to a temperature range of 373 K - 647 K and pressurized to keep it in the liquid state in this temperature range (26). It is known that subcritical water has been used in many processes such as oxidation, extraction (9, 26), solubility (27) and in organic synthesis (28), due to its important properties such as being a green solvent, good availability, cheapness, and having an easily adjustable polarity (29). Subcritical water has been widely used in oxidation processes, because during the subcritical water oxidation process hydroxyl radicals and active oxygen species originate at elevated temperatures and pressures without the addition of an oxidizing agent. Furthermore, if an oxidizing agent such as oxygen, permanganate, hydrogen peroxide, *etc.*, is added to the subcritical medium, this treatment can assist the process to efficiently oxidize various potential pollutants which are difficult to oxidize with conventional methods (8, 30, 31). Subcritical water medium favors the formation of free hydroxyl radicals in the presence of hydrogen peroxide. Hydroxyl radical is a reactive species and attacks to target molecule and provides its mineralization. This feature of subcritical water medium and hydrogen peroxide system indicates that it is a superior method comparing to the conventional methods (7).

Response surface methodology (RSM) is one of the most widely used and accepted chemometric methods. RSM is a useful statistical-based method which is used to optimize the process parameters with a limited number of experiments from many varieties. RSM can also be used to analyze the effects of several independent variables on the response, evaluating the individual and interaction effects of independent variables and to evaluate the performance of a system and the interactions between the experimental parameters in the multivariable chemical process (6, 32, 33).

In the present study, the degradation of HCT using hydrogen peroxide as oxidizing agent in subcritical water medium is reported. The optimal experimental parameters such as temperature, treatment time and concentration of oxidizing agent, and the theoretical maximum total organic carbon (TOC) removal rates were determined using RSM.

EXPERIMENTAL SECTION

Materials

HCT and H_2O_2 were supplied from Sigma-Aldrich (St. Louis, MO, USA). N_2 gas was obtained from Linde gas (Turkey). Ultra-pure water (18 MΩ.cm, 25 °C) was prepared by using Millipore Milli-Q Advantage A10 apparatus (Darmstadt, Germany). 1000 mg/L TOC standard solution was obtained from Merck (Darmstadt, Germany).

Degradation method

The experimental set-up (a home-made reactor, heater with a magnetic stirrer and digital thermometer), which is reported in a previous paper (7), was used to carry out the degradation experiments. Preliminary experiments were done to determine treatment conditions. Further, the central composite design (CCD) method, which is one of the design methods of the RSM, was used to design the experimental conditions. The treatment conditions were lying in the temperature range of 352.5 K - 453.5 K, concentration of oxidizing agent range of 12.7 mM - 147.3 mM, and treatment time range of 12.7 min - 147.3 min as demonstrated in Table 1. The degradation method, which is briefly summarized below, was performed according to Yabalak, 2018 (7). A specific amount of HCT was dissolved in ultra-pure water to prepare 50 ppm of stock aqueous solution of HCT. 150 mL of freshly prepared stock solution was placed in the reactor. In each experiment, a certain amount of H_2O_2, which is displayed in Table 2, was added into the reactor. The reactor was closed, screwed and pressurized to 30 bar by using N_2 gas. The reactor was heated to the target temperature according to the experimental design given in Table 2. After keeping a constant temperature during the treatment time, the reactor was cooled down to the room temperature, depressurized and opened. Finally, at the end of the treatment time, 20 mL of the treated sample was collected and stored at 277 K for TOC analysis.

TOC method

TOC analysis is a common and practical application used to assess the quality of waters by determining its organic content (34). TOC values of the stock solution and treated samples were determined by using a TOC-L analyzer with an ASI-L autosampler (Shimadzu). TOC removal percentages were calculated according to the equation given in the previous work (7).

CCD modeling

RSM, which is a statistical tool that consists of mathematical techniques, enables the optimization of the process (6). CCD is one of the several RSM models and it provides the explanation of the correlation between the experimental variables and responses by designing experiments (7,35). It is based on full factorial or fractional factorial second-order designs and it consists of factorial, central, and axial points in the experimental region (9,36). Design Expert 9.0.6.2 was used to design the three-factor experimental matrix. Table 1 demonstrates the design of the experimental factors along with their coded levels. Independent variables such as temperature, concentration of oxidizing agent, H_2O_2, and treatment time were coded as x_1, x_2, and x_3, respectively. 20 runs from the experimental region were performed and experimental and predicted results of TOC removal efficiency of all runs were displayed in Table 2. Furthermore, the correlation between response and independent variables was enlightened according to the obtained quadratic equation (Eq 1) of the model. In this equation, Y indicates the response (TOC removal percentage), where x_1, x_2, and x_3 depicts the coded independent variables, x_1^2, x_2^2, and x_3^2 represent the square effects. x_1x_2, x_1x_3, and x_2x_3 symbolize interaction effects. The coefficients of linear and quadratic terms indicate their magnitudes (7,9). ANOVA was done and 3D plots were constructed to identify the consistency of the model and to evaluate the interactions between experimental variables.

Table 1: CCD design of the experimental factors along with their coded levels.

Factors	Independent Variables	Coded Levels				
		-1.682	-1	0	1	1.682
x_1	Temperature (K)	352.5	373	403	433	453.5
x_2	Concentration of oxidizing agent (M)	12.7	40	80	120	147.3
x_3	Treatment time (min)	12.7	40	80	120	147.3

RESULTS AND DISCUSSION

The CCD method was employed to identify the effects of system variables on the TOC removal percentage and the relationship between them. Experimental and predicted results of TOC removal percentages are displayed in Table 2.

As clearly seen from Table 2, the highest experimental and predicted TOC removal percentage was obtained in run 20 and run 8 as 85.22% and 87.81%, respectively, while the lowest experimental and predicted TOC removal percentage was obtained in run 11 as 22.51% and 22.63 %, respectively.

Evaluation of the CCD modeling of mineralization of HCT

ANOVA results of the CCD model of the mineralization of HCT were tabulated in Table 3. Statistical analysis, which is based on the evaluation of the Fisher's 'F' tests, and p-values of the model, is crucial to prove the significance of the employed model (7). p and F values of the model were found to be below 0.0001 and 62.88, respectively. The P-value of any model term is desired to be less than 0.05 to claim its significancy (37). In addition, possessing the highest F value indicates a term as the most favourable term of the model. Thus, considering the p and F values of the model, one can say that the employed model is significant and it can be used to designate the effects of the experimental factors on the response, which is the TOC removal percentage. Furthermore, x_1, x_2, x_3, x_1x_2, x_1x_3, x_1^2, and x_3^2 are significant terms of the employed model.

Table 2: Experimental and predicted results of the TOC removal efficiency.

Run	Temperature (K)	Concentration of oxidizing agent (M)	Treatment time (min)	TOC removal, %		Residual	AD, %
				Exp.	CCD pre.		
1	403 (0)	80 (0)	80 (0)	82.89	82.49	0.399	0.48
2	403 (0)	80 (0)	80 (0)	80.94	82.49	1.551	1.92
3	373 (-1)	120 (+1)	120 (+1)	82.06	83.78	1.723	2.10
4	433 (+1)	40 (-1)	40 (-1)	84.01	80.34	3.675	4.37
5	403 (0)	80 (0)	80 (0)	82.36	82.49	0.131	0.16
6	373 (-1)	40 (-1)	120 (+1)	70.99	71.07	0.077	0.11
7	352.5 (-1.682)	80 (0)	80 (0)	38.42	39.33	0.909	2.37
8	403 (0)	147.3 (+1.682)	80 (0)	84.35	87.81	3.460	4.10
9	373 (-1)	120 (+1)	40 (-1)	44.03	39.00	5.028	11.42
10	433 (+1)	120 (+1)	40 (-1)	84.87	82.84	2.029	2.39
11	373 (-1)	40 (-1)	40 (-1)	22.51	22.63	0.116	0.52
12	433 (+1)	120 (+1)	120 (+1)	84.18	82.11	2.068	2.46
13	403 (0)	80 (0)	80 (0)	84.12	82.49	1.629	1.94
14	403 (0)	80 (0)	80 (0)	84.89	82.49	2.399	2.83
15	453.5 (+1.682)	80 (0)	80 (0)	84.60	86.45	1.851	2.19
16	403 (0)	80 (0)	80 (0)	80.22	82.49	2.271	2.83
17	433 (0)	40 (-1)	120 (+1)	80.19	83.27	3.076	3.84
18	403 (0)	80 (0)	12.7 (-1.682)	37.12	42.49	5.370	14.47
19	403 (0)	12.7 (-1.682)	80 (0)	75.71	75.01	0.700	0.92
20	403 (0)	80 (0)	147.3 (+1.682)	85.22	82.61	2.610	3.06

AD: Absolute difference between experimental and predicted values

Table 3: ANOVA results of the CCD model of the mineralization of HCT.

Source	**TOC Removal**				
	Sum of Squares	df	Mean Square	F Value	*p*-value prob > F
Model	7252.12	9	805.79	62.88	< 0.0001
x_1	2680.36	1	2680.36	209.17	< 0.0001
x_2	197.77	1	197.77	15.43	0.0028
x_3	1942.95	1	1942.95	151.63	< 0.0001
x_1x_2	96.19	1	96.19	7.51	0.0208
x_1x_3	1035.58	1	1035.58	80.82	< 0.0001
x_2x_3	6.70	1	6.70	0.52	0.4863
x_1^2	692.08	1	692.08	54.01	< 0.0001
x_2^2	2.10	1	2.10	0.16	0.6939
x_3^2	716.30	1	716.30	55.90	< 0.0001
Residual	128.14	10	12.81		
Lack of Fit	112.03	5	22.41	6.95	0.0264
Pure Error	16.11	5	3.22		

$$Y = 14.01x_1 + 3.81x_2 + 11.93x_3 - 3.47x_1x_2 - 11.38x_1x_3 - 0.91x_2x_3 - 6.93x_1^2 - 0.38x_2^2 - 7.05x_3^2 + 82.49$$ (Eq. 1).

The predicted TOC removal percentages of all runs were obtained by employing CCD. The second-order polynomial equation (Eq. 1) was used for this purpose. Also, using Eq. 1 is a practical way for predicting the response of the system for given levels of system factors. In addition, the coefficient of the coded factors of the equation shows the level of effectiveness of each factor on the TOC removal percentages. Thus, it is clearly seen that temperature is the most effective variable on the TOC removal rates followed by treatment time, while the quadratic effect of the H_2O_2 concentration remains negligible.

Table 4: Regression coefficients of the CCD model.

Regression coefficients			
Standard Deviation	3.58	**R^2**	0.9826
Mean	72.68	**Adjusted R^2**	0.9670
C.V. %	4.92	**Predicted R^2**	0.8768
PRESS	909.56	**Adequate Precision**	25.752

The regression coefficients of a model show its reliability. Table 4 demonstrates the regression coefficients of the employed CCD model. The obtained predicted residual sum of squares (PRESS) value of 909.56 shows that the model adapts each point in the design. The adequate precision value of 25.752 verifies that the model can be applied to navigate the design space (7). Also, the conformity of the model was provided based on the R^2 value of 0.9826. The adjusted R^2 value of 0.9670 represents the amount of variation around the mean. The reasonable agreement of the R^2 value with adjusted R^2 indicate a high correlation level between experimental and predicted values. Further, Figure 2, which depicts the correlation between actual (experimental) and predicted TOC removal values, supports this accordance. Closeness of colored points to the linear line demonstrates the conformity of experimental and predicted values. Thus, Figure 2 shows that both actual and predicted points of the applied method match each other.

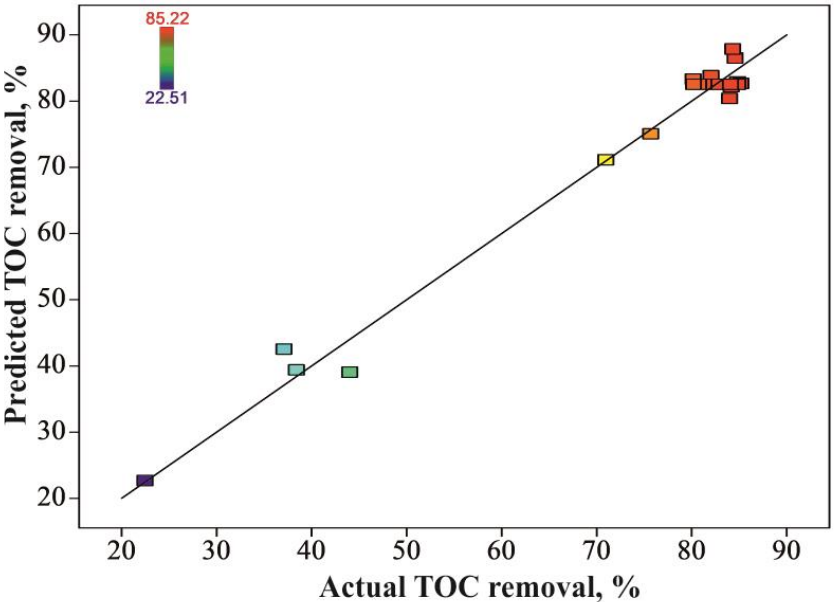


Figure 2: Correlation between actual and predicted values of the TOC removal rates.

Figure 3 shows the cube plot of CCD model of the TOC removal. It is feasible to predict the response in any case that consists of three experimental factors in the working range by using Figure 3. In addition, the evaluation of the further experiments and estimation of the experimental conditions can be performed by the aid of Figure 3. It can be seen from this figure that 83.78 % of TOC removal percentage can be obtained at the highest level of treatment time and H_2O_2 concentration but at the lowest level of temperature. Moreover, almost the same value of TOC removal percentage can be obtained (83.26 %) by increasing the temperature and treatment time to their highest value and decreasing the concentration of H_2O_2 to its lowest value.

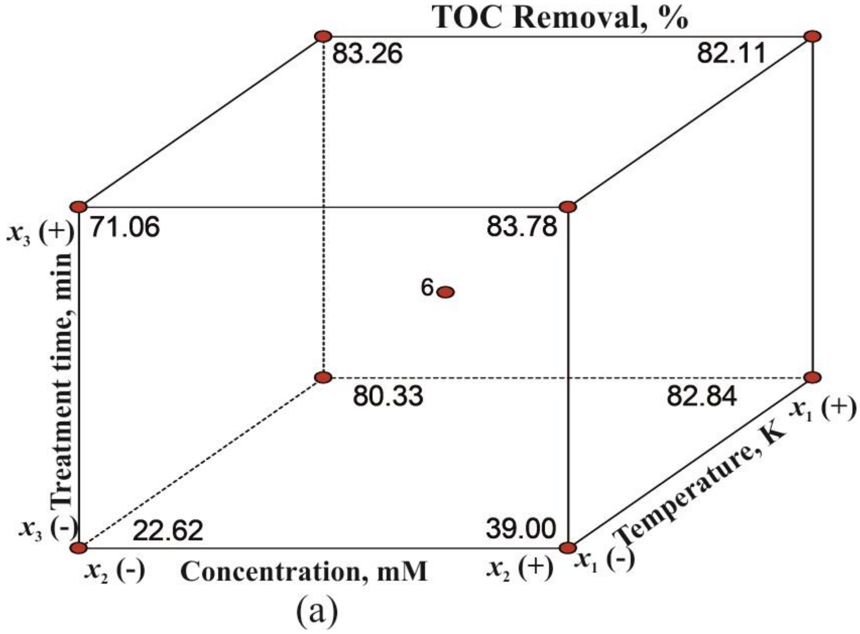


Figure 3: Cube plot of the model.

Binary effects of experimental variables on the response can be demonstrated by using three-dimensional surface plots. Figure 4 shows the binary effects of H_2O_2 concentration and temperature on the TOC removal at the fixed treatment time of 50 min. It is clearly seen that the combined effect of temperature and H_2O_2 concentration increases TOC removal percentages, especially above 413 K, at the fixed treatment time of 50 min. Moreover, 50 min and above treatment times are quite sufficient for formation of hydroxyl and other radicals at above medium levels of temperature and H_2O_2 concentration. Thus, when the reaction medium contains an appropriate amount of H_2O_2, temperature plays the major role in providing these radicals and elevating the mineralization percentage of HCT. The role of H_2O_2 concentration remains minor considering the role of temperature in the above-mentioned conditions. While the effect of temperature increases in its high levels, the effect of H_2O_2 concentration gains importance in the lower level of temperature in the fixed 50 min of treatment time. For example, 69.58% of TOC removal increases to 85.19% by elevating the temperature from 403 K to 433 K at the fixed treatment time of 50 min and H_2O_2 concentration of 80 mM. However, only about 2 % increase is seen in the 83.78% of TOC removal value by increasing H_2O_2 concentration from 40 mM to 120 mM at the fixed treatment time of 50 min and 433 K of temperature. Moreover, when the same enhancement was applied at the same treatment time, about 9% and 16% of enhancement are observed at 403 K and 373 K, respectively.

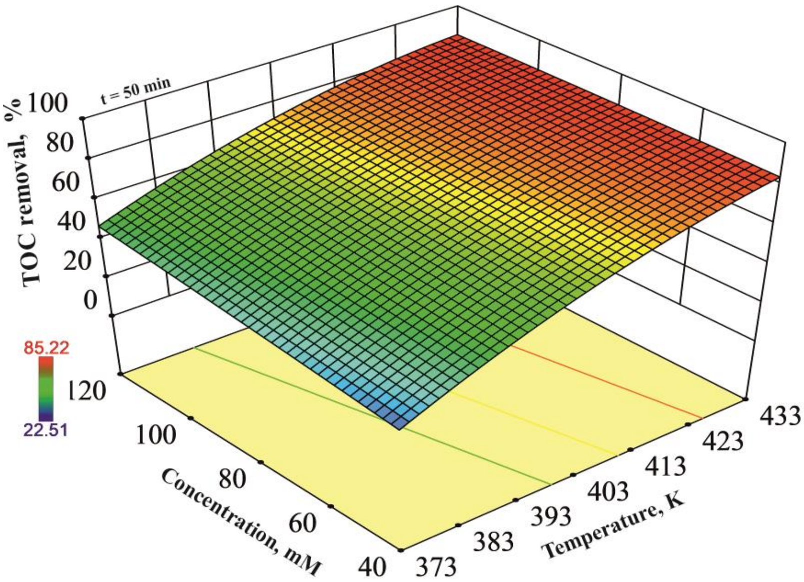


Figure 4: Binary effects of H_2O_2 concentration and temperature on the TOC removal at fixed treatment time of 50 min.

The combined effect of treatment time and temperature on the TOC removal at the fixed H_2O_2 concentration of 40 mM is shown in Figure 5. This effect is quite noteworthy, especially at above the medium level of both temperature and treatment time at the fixed H_2O_2 concentration of 40 mM.

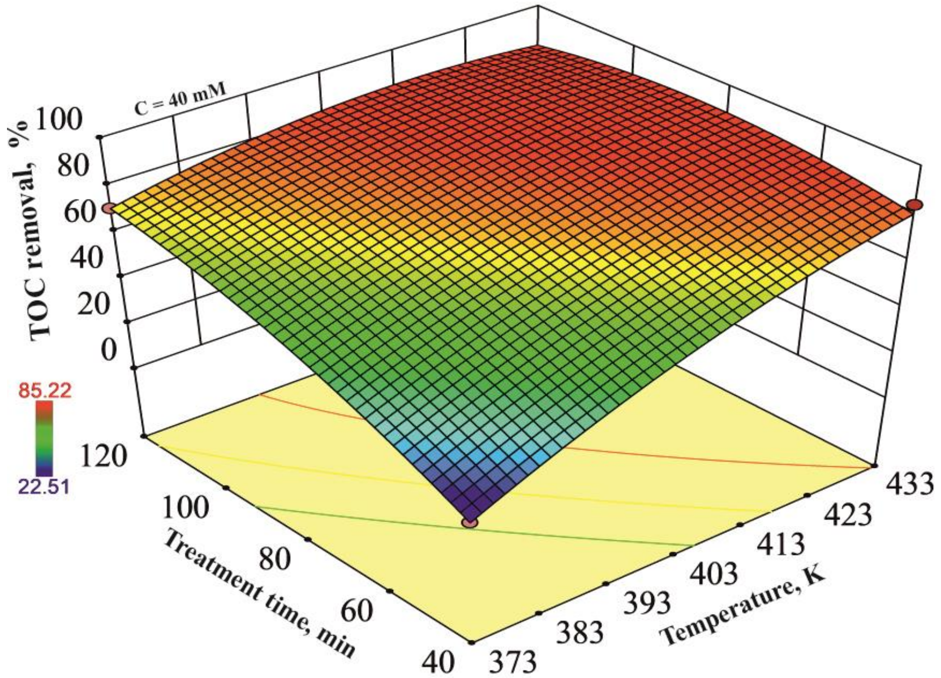


Figure 5: Binary effects of treatment time and temperature on the TOC removal at fixed H_2O_2 concentration of 40 mM.

Alternatively, short treatment time-high temperature and long treatment time-low temperature conditions provide elevated TOC removal rates at the fixed H_2O_2 concentration of 40 mM, according to Figure 5. Based on these results, one can say that adequate free radicals might be formed by keeping treatment time or temperature at specific values. For instance, to obtain 80.34 % of TOC removal, 433 K of temperature and 40 min of treatment time is required at the fixed H_2O_2 concentration of 40 mM. The same efficiency can be obtained at 390.5 K of temperature and 120 min of treatment time at the same H_2O_2 concentration.

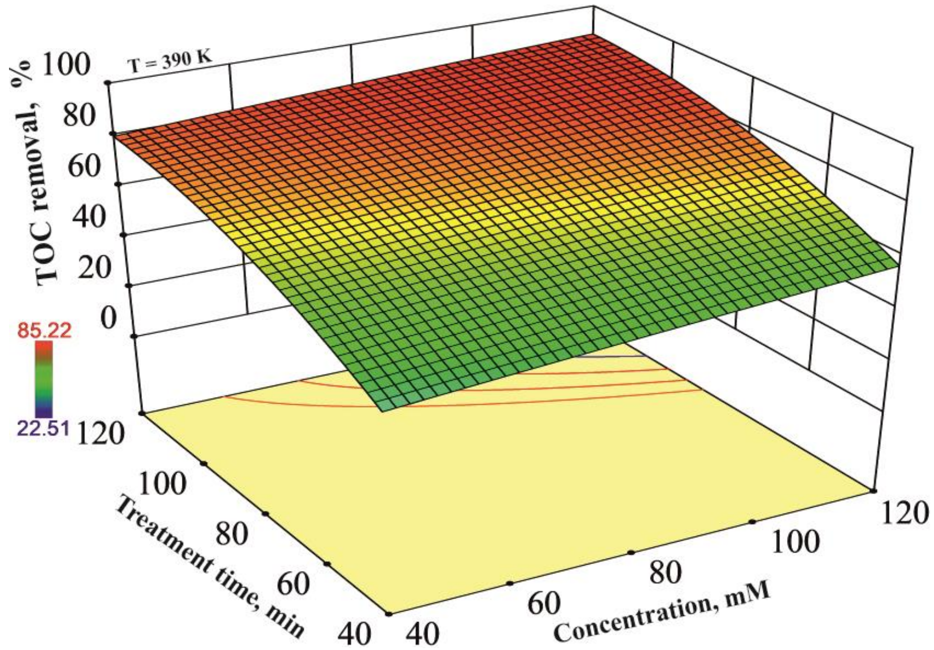


Figure 6: Binary effects of treatment time and H_2O_2 concentration on the TOC removal at the fixed temperature of 390 K.

Binary effects of treatment time and H_2O_2 concentration on the TOC removal at the fixed temperature of 390 K are demonstrated in Figure 6. This figure shows that, while moderate TOC removal percentages can be obtained at low levels of H_2O_2 concentration and treatment time at the fixed temperature of 390 K, the treatment time must be increased to obtain high TOC removal percentages. Further, increasing the H_2O_2 concentration at moderate and upper levels of treatment time at the fixed temperature of 390 K only has little influence on the TOC removal percentages. It may be attributed to the fact that, while the role of H_2O_2 concentration is crucial in the mineralization of HCT, increasing the H_2O_2 concentration above a specific level does not directly elevate degradation rates due to possible self-quenching of free radicals present in the reaction medium (7). According to Figure 6, this method should be regarded as superior to the conventional methods in terms of achieving the same efficiency with different application conditions. Thus, the possibility of achieving high efficiency of TOC removal of HCT at long treatment time and low temperature or at short treatment time and high temperature provides important advantages in reducing the operating costs on the industrial scale (large scale applications).

CONCLUSIONS

Mineralization of HCT was effectively achieved by using subcritical water oxidation as an applicable, efficient and environmentally friendly method, and by using H_2O_2 as a green oxidizing agent. Subcritical water favoured the formation of free radicals, and in the presence of H_2O_2, at an adequate treatment time. Thus, it can be said that on the basis of the obtained results, subcritical water and H_2O_2 have synergetic effects on the TOC removal of HCT. High TOC removal rate (85.22%) proved the reliability of this method as well as its applicability in the mineralization process of similar contaminants. Moreover, the CCD method was performed and the interaction of experimental variables as well as their effects on the response was evaluated. Temperature, followed by treatment time, were found to be effective experimental factors on the efficiency of the method. Also, the obtained high TOC removal rates in the short treatment time show that the applied method is a time-saving method.

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