Available online on www.ijpqa.com
International Journal of Pharmaceutical Quality Assurance 2019; 10(1); 90-99
doi: 10.25258/ijpqa.10.1.15
ISSN 0975 9506

Research Article

Optimized Conditions for Pharmaceuticals and Personal Care Products Removal by Ozonation Using Response Surface Methodology

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Received: 31st Dec, 18; Revised: 14th Feb, 19, Accepted: 25st Feb, 19; Available Online: 25th Mar, 2019

ABSTRACT
This study investigated the optimum conditions for the total pharmaceutical and personal care products (PPCPs) removal from PPCPs-contaminated tap water using ozonation treatment. The optimum conditions for maximum PPCPs removal were determined through a Box-Behnken Design (BBD). Three operational variables, i.e. PPCPs concentration (1-600 µg/L, retention time15-30 min and pH 6-9 units) were investigated by setting PPCPs removal concentration as the maximum. The optimum conditions were selected with the highest desirability of 0.967 using the maximum concentration of PPCPs and highest removal of PPCPs from the water (95-100 %) with the minimum retention time for 15 min and the pH was set at pH 8.9. From a validation test of the optimum conditions, it was found that the maximum PPCPs removal from contaminated tap water was closely to the predicted ones with less than 5% error for all the four compounds which give an evidence that ozonation is a good technique to remove PPCPs from water stream.

Keywords: Pharmaceuticals and personal care products, Ibuprofen, Ketoprofen, 17α-ethinylestradiol, Galaxolide, Ozonation, optimization, validation.

INTRODUCTION

Micropollutants are trace organic contaminants or metals found in waters at very low concentrations (billionths to millionths of a gram per liter). The concern from the occurrence of the micropollutant is associated with a number of negative short- and long-term effects, endocrine disrupting effects and antibiotic resistance of microorganisms[1]. Also, micropollutants are commonly present in water at trace concentrations, ranging from a few ng/L to several µg/L. The 'low concentration' and diversity of micropollutants not only complicate the associated detection and analysis procedures but also create challenges for water and wastewater treatment processes. One of the major threats to water quality is chemical pollution, especially from the petrochemical, pesticide and pharmacy industries, among others[2].

Pharmaceuticals and Personal care products (PPCPs) which is one type of the micropollutant are a varied group of common household substances used for health, beauty and cleaning purposes. These include medicines, pills, disinfectants, fragrances, preservatives and UV filters. Some of them are considered chemicals of emerging concern due to their presence and negative impact on aquatic ecosystems, specially related to endocrine disruption, human health and reproductive disorders. The entry of those chemicals to water bodies occurs mainly through the sewage effluents from wastewater treatment plants due to their incomplete or inefficient removal[3]. The largest number of PPCPs documented in many studies as emerging pollutants were found in wastewater treatment plant effluents. However, there is a lack of information regarding the presence of emerging pollutants from PPCPs in developing countries[4].

Current methods applied to remove organic components from wastewater include adsorption on activated carbon, chemical oxidation, electrochemical, and many other technologies. Even so, these methods present certain disadvantages, such as low efficiency and high cost[5]. Therefore, new green technologies are being pursued as alternative wastewater treatment methods for the removal of toxic organic pollutants, such as ozonation[6] which considered an environmentally friendly engineering technology to remove the PPCPs from the water stream as there is many advanced oxidation processes (AOPs) have been used for wide range of treatment[7].

Ozonation consistently reduced the cytotoxicity of both the full strength and the organic extracts of all tested wastewaters more than chlorination[8]. Special attention is given on WWTPs since pharmaceuticals usually exit secondary treatment unaffected and, therefore, they need to be treated in subsequent stages. Ozone is a strong oxidant that either decomposes in water to form hydroxyl radicals which are stronger oxidizing agents than ozone itself, one of the first studies which showed the efficiency of ozonation for removal of micropollutants in biological treated wastewater was by[9] RSM is a collection of statistical and mathematical methods which are beneficial for developing, improving and optimizing a process. The

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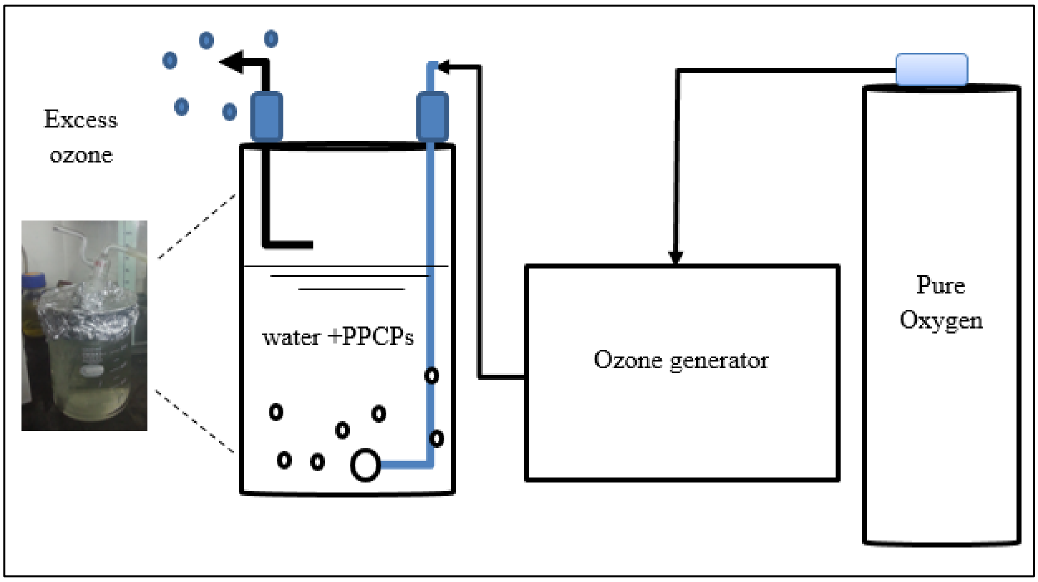

Figure 1: Schematic diagram for ozone experimental set-up.

Study Type	Response Surface		**Experiments**	54			
Initial Design	Box Behnken		**Blocks**	No Blocks			
Design Model	Quadratic						
Response	**Name**	**Units**	**Obs**	**Minimum**	**Maximum**	**Trans**	**Model**
Y1	Removal HHCB	%	54	66.00	100.00	None	Quadratic
Y2	Removal EE	%	54	67.00	100.00	None	Quadratic
Y3	Removal IBU	%	54	67.00	100.00	None	Quadratic
Y4	Removal KETO	%	54	75.00	100.00	None	Linear
Factor	**Name**	**Units**	**Type**	**Low Actual**	**High Actual**	**Low Coded**	**High Coded**
A	pH		Numeric	6.00	9.00	-1.000	1.000
B	time	min	Numeric	15.00	30.00	-1.000	1.000
C	con. ibu	mg/l	Numeric	25.00	600.00	-1.000	1.000
D	con. keto	mg/l	Numeric	15.00	60.00	-1.000	1.000
E	con.hhcb	mg/l	Numeric	100.00	600.00	-1.000	1.000
F	con. EE2	mg/l	Numeric	1.00	2.00	-1.000	1.000

Figure 2: Variables and their levels in the experimental design.

$$Y_1 = \begin{bmatrix} 91.17 + 8.83A + 0.83B - 2.08C + 2.58D - 1.21E - 2.50F - 1.4A^2 - 1.25B^2 - 0.042C + 0.54D^2 \\ +0.37E^2 - 0.29F - 1.50AB + 0.6AC - 2.31AD + 0.87AE + 3.38AF + 0.50BC - 1.50BD \\ -0.50BE + 3.50BF + 1.12CD + 1.75CE + 0.13CF + 0.63DE + 0.37DF + 2.50EF \end{bmatrix} \quad 1$$

$$Y_2 = \begin{bmatrix} 92.00 + 7.25A + 0.37B - 0.42C + 0.083D - 1.17E - 0.33 \times 3.96A^2 + 1.29B^2 + 0.79C^2 \\ +3.29D^2 - 0.46F^2 + 1.88AB - 1.13AC - 1.44AD + 1.25AE + 4.38AF + 1.75\,BC \\ +1.88BD + 3.25\,BE + 1.75BF - 0.88CD - 0.50CE + 1.50CF + 2.25DE + 2.13DF - 0.75E \end{bmatrix} \quad 2$$

$$Y_3 = \begin{bmatrix} 92.67 + 8.21A + 1.08B - 3.96C - 1.79D - 1.33E + 0.71F - 2.93A + 0.69B^2 - 0.43C^2 \\ -0.68D^2 + 0.44E^2 + 0.32F2 - 1.75AB + 2.63AC + 2.25AD - 0.25AE + 0.12AF - 1.38BC \\ -0.75B\,D + 2\,B0.88BF + 0.37CD - 2.38CE - 0.25CF + 0.50DE + 1.38D + 1.12EF \end{bmatrix} \quad 3$$

$$Y_4 = [94.20 + 6.12A + 0.58B - 0.63C + 0.87D + 0.42E + 0.33F] \quad 4$$

main advantage of RSM is to reduce the number of experimental trials required to estimate multiple parameters and their interactions[10]. The DOE methodology is usefully applied in the development of appropriate wastewater treatment technologies and in considering the effects of operational parameters on the remediation process[11]. The optimization of the operating conditions for maximum PPCPs removal by ozonation will be conducted. The optimization step was undertaken to obtain the optimum conditions for PPCPs removal
from water contaminated with it. For the PPCPs optimized removal the conditions were set for maximum removal using the Response Surface Method (RSM) which is an efficient statistical tool that can be used for modelling and optimization of more than one process variable and have been used in many researches and studies like[12] and Using 3D response surface plots, one can better understand the relationship between process variables and responses of experiments.

The optimization was carried out on the variable parameters of PPCPs concentration in tap water, ozonation retention time and pH. The optimization was carried out using a model of the response surface method (RSM) in the design of experiment (DOE) through the Box–Behnken design (BBD). The aim of the optimization of ozonation system is to determine the optimal values for such factors as PPCPs concentration, pH and ozonation retention time in order to improve the treatment efficiency also a validation run was done under the optimum conditions to validate the optimized condition. To reduce the laboratory experiments and to save time and cost, the application of RSM is a recommended method for wide range of studies, especially for the water treatment process. Recently, RSM has been applied to the optimization of several water treatment processes, such as ultrafiltration[13], nano-porous membranes[14] and ozonation[15]. Since the optimization of ozonation treatment is rare, in this study we have adopted RSM

Table 1: ANOVA analysis of the quadratic model for HHCB removal from water.

Source	Sum of Squares	Degrees of Freedom	Mean square	F-Value	Prob> F	
Model	2789.15	27	103.30	2.17	0.0260	significant
A	1872.67	1	1872.67	39.32	< 0.0001	
B	16.67	1	16.67	0.35	0.5592	
C	104.17	1	104.17	2.19	0.1512	
D	160.17	1	160.17	3.36	0.0781	
E	35.04	1	35.04	0.74	0.3988	
F	150.00	1	150.00	3.15	0.0876	
A^2	21.87	1	21.87	0.46	0.5039	
B^2	16.07	1	16.07	0.34	0.5663	
C^2	0.018	1	0.018	3.750E-004	0.9847	
D^2	3.02	1	3.02	0.063	0.8032	
E^2	1.45	1	1.45	0.030	0.8630	
F^2	0.88	1	0.88	0.018	0.8932	
AB	18.00	1	18.00	0.38	0.5440	
AC	3.13	1	3.13	0.066	0.7998	
AD	85.56	1	85.56	1.80	0.1917	
AE	6.13	1	6.13	0.13	0.7228	
AF	91.13	1	91.13	1.91	0.1783	
BC	2.00	1	2.00	0.042	0.8392	
BD	18.00	1	18.00	0.38	0.5440	
BE	4.00	1	4.00	0.084	0.7743	
BF	98.00	1	98.00	2.06	0.1633	
CD	10.13	1	10.13	0.21	0.6486	
CE	24.50	1	24.50	0.51	0.4796	
CF	0.25	1	0.25	5.250E-003	0.9428	
DE	3.13	1	3.13	0.066	0.7998	
DF	1.13	1	1.13	0.024	0.8790	
EF	50.00	1	50.00	1.05	0.3150	
Residual	1238.19	26	47.62			
Lack of Fit	867.35	21	41.30	0.56	0.8426	not significant
Cor Total	4027.33	53				
Std. Dev.	6.90	R^2	0.6926			
Mean	90.22	Adj R^2	0.3733			
Adeq Precision	5.832					Model is desirable

Table 2: ANOVA analysis of the quadratic model for EE_2 removal from water.

Source	Sum of Squares	Degrees of Freedom	Mean square	F-Value	Prob> F	
Model	2256.56	27	83.58	3.07	0.0027	Significant
A	1261.50	1	1261.50	46.31	< 0.0001	
B	3.38	1	3.38	0.12	0.7277	
C	4.17	1	4.17	0.15	0.6989	
D	0.17	1	0.17	6.118E-003	0.9383	
E	32.67	1	32.67	1.20	0.2835	
F	2.67	1	2.67	0.098	0.7569	
A^2	161.16	1	161.16	5.92	0.0222	
B^2	17.16	1	17.16	0.63	0.4346	
C^2	6.45	1	6.45	0.24	0.6307	
D^2	111.45	1	111.45	4.09	0.0535	
E^2	48.29	1	48.29	1.77	0.1946	
F^2	2.16	1	2.16	0.079	0.7805	
AB	28.13	1	28.13	1.03	0.3189	
AC	10.13	1	10.13	0.37	0.5474	
AD	33.06	1	33.06	1.21	0.2807	
AE	12.50	1	12.50	0.46	0.5041	
AF	153.13	1	153.13	5.62	0.0254	
BC	24.50	1	24.50	0.90	0.3517	
BD	28.13	1	28.13	1.03	0.3189	
BE	169.00	1	169.00	6.20	0.0195	
BF	24.50	1	24.50	0.90	0.3517	
CD	6.13	1	6.13	0.22	0.6393	
CE	2.00	1	2.00	0.073	0.7886	
CF	36.00	1	36.00	1.32	0.2608	
DE	40.50	1	40.50	1.49	0.2337	
DF	36.13	1	36.13	1.33	0.2600	
EF	4.50	1	4.50	0.17	0.6877	
Residual	708.27	26	27.24			
Lack of Fit	446.27	21	21.25	0.41	0.9341	Not significant
Cor Total	2964.83	53				
Std. Dev.	5.22	R^2	0.7611			
Mean	93.39	Adj R^2	0.5130			
Adeq Precision	7.999					Desirable model

using the Box-Behnken Design (BBD) to optimize the performance of the ozonation of water stream contaminated with PPCPs. In the present study, we used tap water spiked with PPCPs with different concentrations and then ozonated with different retention time using ozone with concentration of 4 mg/L to remediate the water contaminated with different PPCPS concentrations. The aim is to maximise the PPCPs removal efficiency from water using RSM through a Box-Behnken experimental design by optimising the PPCPs concentration, retention time and pH value.

MATERIALS AND METHODS

Ozonation setup operation

The ozonation system was performed by an ozone generator (IN USA, AC -2025) using pure oxygen tube with a constant ozone concentration of 4 mg/L as shown in figure 1 that shows the schematic diagram of the ozone system used for the treatment process and the ozone generation. The water-PPCPs was collected in (1 L) glass reactor and spiked with the PPCPs ranged between 2-600 µg/L for the tap water (Al-Qaim et al. 2014). The water-PPCPs mixture was stirred for 20 min at 2800 rpm to obtain a homogeneous solution in the system. Once the water-PPCPs completely mixed, ozone treatment was commenced by bubbling for duration between 15, 30 and 60 min and pH were in the range of 6.5-9 depending on test type.

Sample preparation

Samples of the optimization study process were prepared by spiking the PPCPs with different concentration. For both Ibuprofen and Galaxolide, the working concentration were 600 µg/L[17,18] and for the ketoprofen, it was 60 µg/L[19], finally for the 17α-ethinylestradiol was 2

Table 3: ANOVA analysis of the quadratic model for IBU removal from water.

Source	Sum of Squares	Degrees of Freedom	Mean square	*F*-Value	Prob>*F*	
Model	2655.65	27	98.36	2.30	0.0187	Significant
A	1617.04	1	1617.04	37.75	< 0.0001	
B	28.17	1	28.17	0.66	0.4248	
C	376.04	1	376.04	8.78	0.0064	
D	77.04	1	77.04	1.80	0.1915	
E	42.67	1	42.67	1.00	0.3275	
F	12.04	1	12.04	0.28	0.6005	
A^2	88.34	1	88.34	2.06	0.1629	
B^2	4.96	1	4.96	0.12	0.7364	
C^2	1.91	1	1.91	0.045	0.8346	
D^2	4.76	1	4.76	0.11	0.7415	
E^2	2.03	1	2.03	0.047	0.8293	
F^2	1.05	1	1.05	0.025	0.8768	
AB	24.50	1	24.50	0.57	0.4563	
AC	55.12	1	55.12	1.29	0.2670	
AD	81.00	1	81.00	1.89	0.1808	
AE	0.50	1	0.50	0.012	0.9148	
AF	0.13	1	0.13	2.918E-3	0.9573	
BC	15.13	1	15.13	0.35	0.5575	
BD	4.50	1	4.50	0.11	0.7485	
BE	64.00	1	64.00	1.49	0.2326	
BF	6.13	1	6.13	0.14	0.7084	
CD	1.13	1	1.13	0.026	0.8725	
CE	45.12	1	45.12	1.05	0.3142	
CF	1.00	1	1.00	0.023	0.8797	
DE	2.00	1	2.00	0.047	0.8306	
DF	15.13	1	15.13	0.35	0.5575	
EF	10.13	1	10.13	0.24	0.6309	
Residual	1113.83	26	42.84			
Lack of Fit	722.50	21	34.40	0.44	0.9158	Not significant
Cor Total	3769.48	53				
Std. Dev.	6.55	R^2	0.7045			
Mean	91.52	Adj R^2	0.3977			
Adeq Precision	6.012					Desirable model

Table 4: ANOVA analysis of the linear model for KET removal from water.

Source	Sum of Squares	Degrees of Freedom	Mean square	F-Value	Prob> F	
Model	943.13	6	157.19	5.47	0.0002	Significant
A	900.37	1	900.37	31.35	< 0.0001	
B	8.17	1	8.17	0.28	0.5963	
C	9.37	1	9.37	0.33	0.5705	
D	18.37	1	18.37	0.64	0.4278	
E	4.17	1	4.17	0.15	0.7050	
F	2.67	1	2.67	0.093	0.7619	
Residual	1349.63	47	28.72			
Lack of Fit	1252.30	42	29.82	1.53	0.3391	Not significant
Cor Total	2292.76	53				
Std. Dev.	5.36	R^2	0.4113			
Mean	94.20	Adj R^2	0.3362			
Adeq Precision	7.861					Desirable model

µg/L[20]. Depending on the DOE parameters that limits the experiments to 54 runs for the optimization study. The samples were ozonated for different retention time (15, 22.5 and 30 min). three replicates were taken to insure the results.

Optimization conditions with the Box-Behnken

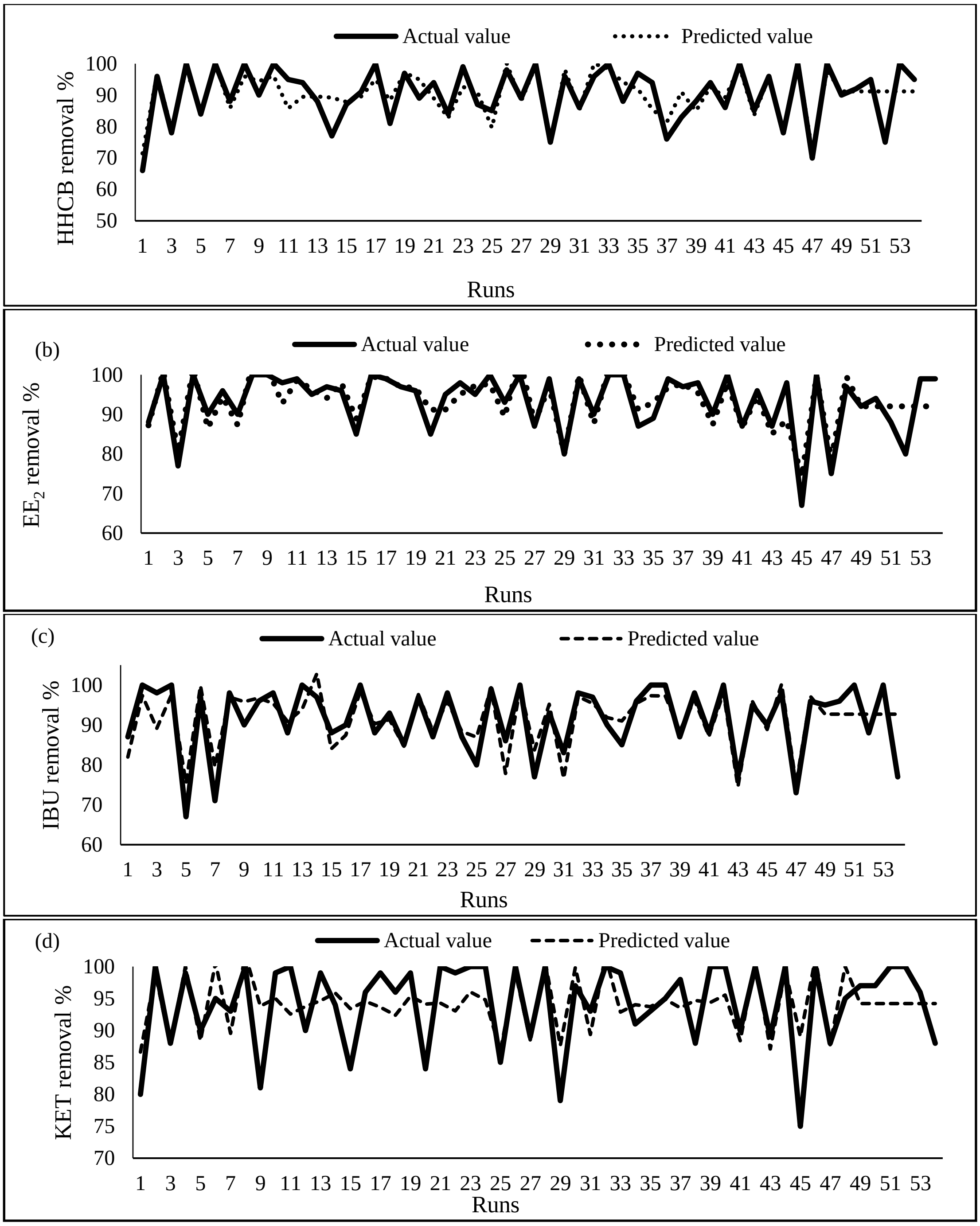

Figure 3: Comparative performance of %PPCPs removal obtained in experiments (actual value) with that estimated by the Box–Behnken (predicted value) per run (a) HHCB removal (b) EE2 removal (c) IBU removal (d) KET removal.

In the optimization study of the ozonation system, the PPCPs concentration in water was set by using a BBD. The interaction between the main factors of PPCPs concentration, retention time and pH, and the response of PPCPs removal efficiency in contaminated water were investigated. The results were then analysed to develop an appropriate model for these factors. The variability factors included in the design were PPCPs concentrations of IBU within 25-600 µg/L, KET (15-60 µg/L), HHCB (100-600 µg/L) and EE_2 (1-2 µg/L) as in mixture exposure and the ozonation retention time 15, 22.5 and 30 min, and for the pH were 6, 7.5 and 9 units as shown in figure 2 that shows the variables and the response as shown in the software.

RESULTS AND DISCUSSION

Evaluation by BBD

The effects of PPCPs concentration, retention time, and pH value on PPCPs removal from the contaminated water was investigated by using BBD. The design simulated 54 total experiment including five replicates to assess the error magnitude that occurs randomly. BBD was used for the statistical design of experiments and data analysis. In the optimization, the responses were coupled to selected

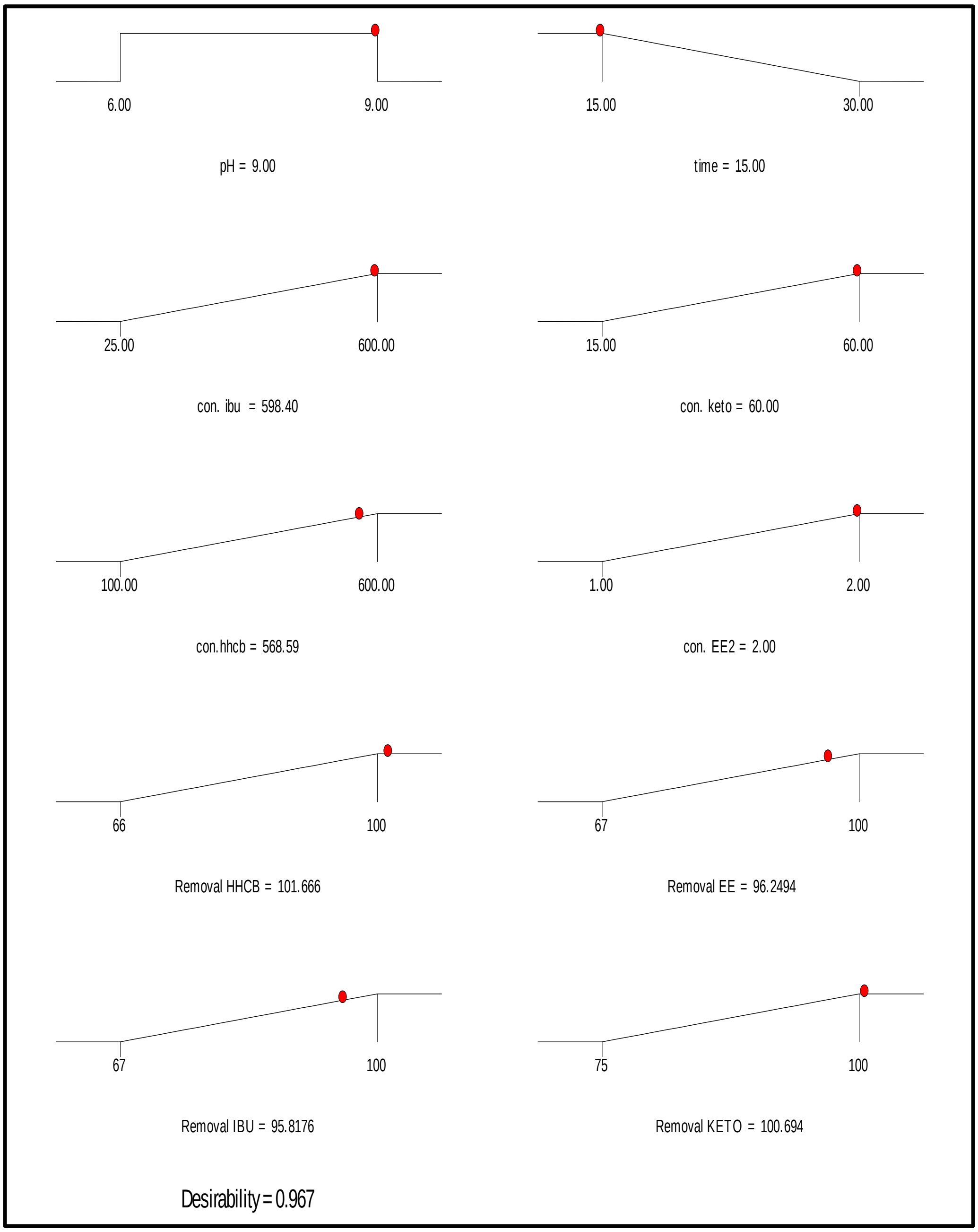

Figure 4: The range of factors and the predicted results of PPCPs removal from water in the optimum conditions.

variables by linear or quadratic models. The mathematical relations between the responses and these variables can be represented by quadratic models for galaxolide, ibuprofen, and 17ethinylestradiol Eq. (1), (2) and (3) while Ketoprofen was represented by liner model as shown in Eq. (4)

with, Y_1= Removal of HHCB (%), Y_2= Removal of EE_2 (%), Y_3= Removal of IBU (%), Y_4= Removal of KET (%), A= pH, B = retention time in min, C = IBU concentration in µg/L, D = KET concentration in µg/L, E = HHCB concentration in µg/L, F = EE_2 concentration in µg/L.

Design Expert_ software (version 6.0.10, Stat-Ease, USA) was used to simulate the experimental run and optimize PPCPs removal The ANOVA results for the PPCPs removal from water are presented in Table 1 to table 4. It indicates that the equation effectively represents the relationship between the response and the significant input variables. The associated *p*-value is used to estimate whether *F* is large enough to indicate statistical significance. The *p* values lower than 0.05 indicates that the model is statistically significant at the 95% probability level. For optimization of a response surface, a model of “good fit” is needed to avoid poor or unclear results.

From the results, it was found that all the models are (Desirable model) for the linear and the quadratic model. The ANOVA results showed significant (P< 0.05) response surface models with good R2 results.

Optimization of operational conditions

The model was used to determine the PPCPs removal from water with the optimal conditions. A Comparative plot of %PPCPs removal obtained in the 54 experiments runs (actual value) with the estimated by the Box–Behnken

Table 5: The different range of the desirability.

Option	Concentration (µg/L)				pH	RT	Removal (%)				Desirability
	HHCB	EE_2	IBU	KET			HHCB	EE_2	IBU	KET	
1	578.65	2.00	600.00	60.00	8.9	15.01	101	96	95	100	0.967
2	526.48	1.86	599.99	60.00	8.8	15.00	100	94	95	99	0.937
3	600.00	1.98	599.99	60.00	8.5	19.02	101	100	92	99	0.936
4	584.93	1.80	598.03	60.00	9.0	16.26	102	95	94	100	0.936
5	599.99	2.00	600.00	49.21	9.0	16.55	101	95	93	100	0.926
6	600.00	2.00	360.91	60.00	8.7	15.23	99	98	96	100	0.926
7	488.86	2.00	404.15	50.96	9.0	15.00	98	95	98	100	0.884
8	355.14	1.89	380.20	60.00	9.0	18.72	99	98	99	101	0.847
9	331.79	1.51	600.00	57.04	8.9	15.00	98	91	99	99	0.820
10	600.00	1.86	230.58	59.83	8.6	24.88	100	107	98	100	0.788

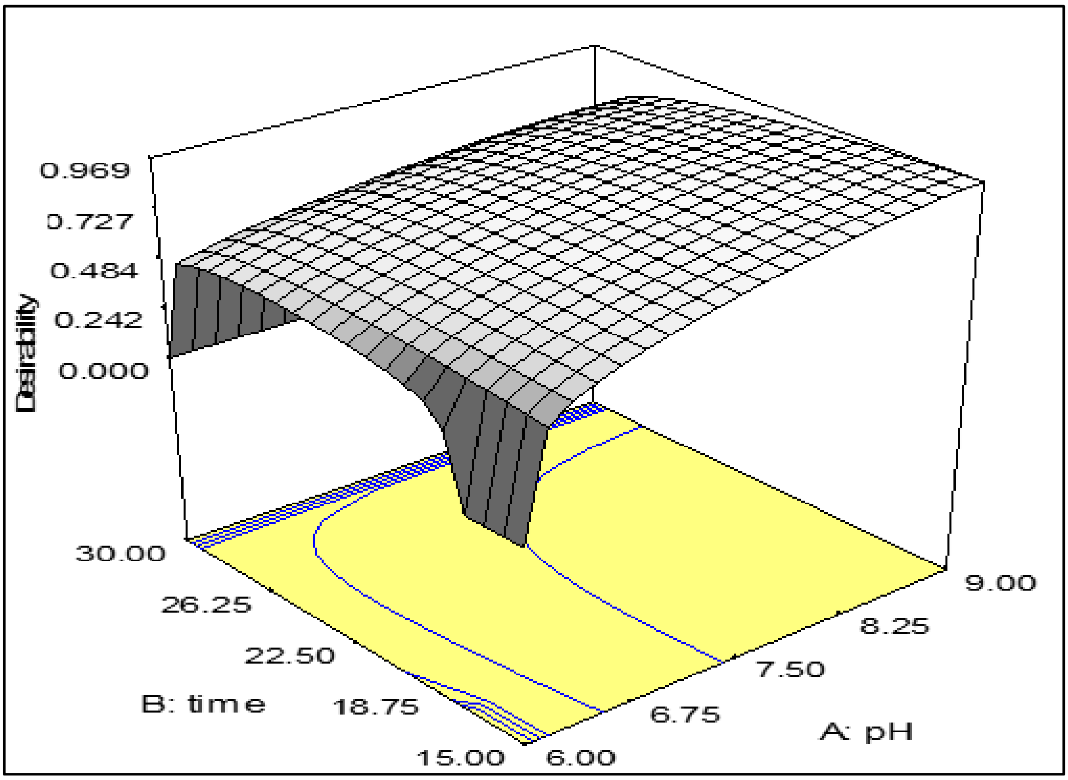

Figure 5: Optimum conditions for PPCPs removal from water.

(predicted value) shows that the residual behaviour followed a normal distribution, which is the more important assumption for checking statistical modelling as shown in figure 3, it can be noted that the values calculated using the predictive quadratic and liner model were in good agreement with the experimental values with a satisfactory correlation between these values. Therefore, the developed model is suitable for predicting the efficiency of PPCPs removal from water under the investigated conditions.

Desirability of optimization model

The target of optimizing the process was to find the optimum operation conditions leading to maximum PPCPs removal from water. The desirability function methodology was used for this optimization. When operating the ozonation process with the variables of PPCPs concentration, retention time and pH were set within a maximum concentration of PPCPS, pH also maximum value and the ozonation time is was minimized. By using the function of numerical optimization in the Design Expert software, we found a desirability of 0.967 for the maximum PPCPs removal efficiencies as shown in table 5 and figure 4 that shows the different range of the desirability and display the conditions of the optimization process.

The 3D response surface plots show how PPCPs removal from water for HHCB (response variable Y_1), EE_2 (response variable Y_2), IBU (response variable Y_3) and KET (response variable Y_4) relates to the factors of pH (*A*), RT (*B*), and concentration of PPCPs (*C, D, E, F*) for IBU, KET, HHCB and EE_2 respectively through the quadratic model equations for HHCB, EE2 and IBU, and linear model for KET, as mentioned before. Figures 5 shows the 3D surface plot of the effect of pH (*A*), RT (*B*) and PPCPs concentration (*C, D, E, F*) on PPCPs removal from water. It can be seen that PPCPs concentration within the maximum concentration and more retention time with higher pH gave an increase in the response of removing

PPCPs for the water. It is generally believed that the longer retention time (RT) of an ozonation operation equal to 30 min and higher pH equal to pH 9 leads to higher PPCPs removal from the water. Appendix C shows the effect of different factors on the PPCPs removal.

CONCLUSION

The optimization of PPCPs removal was performed by using the Box-Behnken Design. The results show that pH value was the most significant factor for the process, due to the releasing of the OH radicals in the water which are non-selective oxidation agent. The removal of PPCPs was significantly affected by the factors used (pH, the concentration of PPCPs and the ozonation retention time). The coefficients of determination (R2) for the model were a good value with the probability values ($P < 0.05$) demonstrating significance for the regression model to predict the responses. The experimental values were close to the predicted theoretical values, indicating that the models could be validated for the optimization of PPCPs removal from water. The optimum conditions of the process were selected with the highest desirability of 0.967 using the maximum concentration of PPCPs and highest removal of PPCPs from the water (95-100 %) with the minimum retention time for 15 min and the pH was set at pH 8.9.

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