

## Optimization studies for catalytic ozonation of cephalexin antibiotic in a batch reactor

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### ABSTRACT

This study examines the effect of pH of solution, cephalexin (CEX) concentration, and O<sub>3</sub> dosage on removal of CEX by catalytic ozonation. All three parameters were found to exert a significant effect on the removal of cephalexin and on the enhancement in biodegradability of solution. The operating conditions were optimized using response surface methodology (RSM) and artificial neural network (ANN). Both RSM and ANN models were found capable of predicting removal of CEX during catalytic ozonation. Simultaneous optimization of two responses (chemical oxygen demand (COD) removal and CEX removal) was carried out using genetic algorithm based multiobjective optimization. Non-dominated Pareto optimal solutions provided the range of optimum conditions for the catalytic ozonation process. The optimized values of pH (9.7), ozone supply (34.5 mg/L), and CEX concentration (33.6 mg/L) using GA multiobjective optimization corresponded to complete conversion of CEX with 72% removal of COD.

**Key words** | activated carbon, artificial neural network, cephalexin, multiobjective optimization, ozonation, response surface methodology

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### INTRODUCTION

Effluents from the pharmaceutical industry and hospitals inject a considerable amount of water pollution into the receiving water streams or rivers. Many of these pharmaceutical compounds are resistant to biodegradation. The persistence of pharmaceutical compounds in the aquatic environment may induce a generation of resistant bacterial strains. These resistant bacterial strains may transmit to the human population and cause diseases (van der Helm *et al.* 2009; Liu *et al.* 2011). Fat-soluble pharmaceuticals may bio-accumulate into the body of aquatic species such as fish at much higher concentrations than in the water source. These bioaccumulated chemicals may transfer to the human population during consumption of such aquatic animals as a food. We used cephalexin (CEX) antibiotic as a model compound for pharmaceuticals and investigated its removal by catalytic ozonation. CEX is prescribed for bacterial infections like tonsillitis, bronchitis, skin diseases, ear infections and urinary tract diseases. CEX is available on the market under different names such as Ceporex,

Keflex, and Novolexin. CEX was listed among the top 200 prescriptions around the world in 2003 (Lai & Wu 2003).

Few studies have investigated the removal of CEX from aqueous solutions (Guo *et al.* 2010; Liu *et al.* 2011). Liu *et al.* (2011) compared the adsorption capacity of two activated carbons for the removal of CEX from solution. According to their study, Fe<sup>+3</sup>/Cu<sup>+2</sup>-loaded activated carbon adsorbed more CEX compared to pure activated carbon. Possibly Fe<sup>+3</sup>/Cu<sup>+2</sup> induced the attachment of CEX onto activated carbon. Another study, however, illustrated inadequate efficiency of ultrasonic radiations to degrade CEX in solution. A precise report about removal of CEX by catalytic ozonation is scarce. Investigating the ozonation of CEX in the presence of activated carbon may broaden the role of this technique in removing such types of compounds. Activated carbon is a reliable adsorbent due to its high adsorption capacity and is used in widespread applications to treat effluents from both domestic and commercial sources (Wu *et al.* 2008). However, the adsorption capacity of activated carbon

shrinks quickly at near saturation point. The saturated activated carbon frequently requires replenishment or regeneration that causes shutdown of absorber columns. A combination of ozone and activated carbon may extend the life of carbon adsorbent via *in situ* regeneration. The decomposition of ozone into oxidant radicals is plausible when dissolved ozone adsorbs onto the carbon surface (Beltrán *et al.* 2006; Qi *et al.* 2008). The ozone/activated carbon combination is expected to remove CEX efficiently from solution.

Response surface methodology (RSM) is helpful to optimize the desired responses in a minimum set of experiments (Rashid *et al.* 2009; Basha *et al.* 2012). The development of a regression model and optimization of input are possible using RSM. RSM can also estimate the effect of individual input variables on the desired response. Artificial neural network (ANN) is another optimization tool that can predict response accurately. ANN is a data-driven self-adaptive technique that predicts an unseen response correctly based on information of training data (Khashei & Bijari 2010). An ANN model has been applied in the removal of hazardous compounds from wastewater using advanced oxidation (Durán *et al.* 2006; Aleboye *et al.* 2008; Elmolla *et al.* 2010), and physicochemical (Syu *et al.* 2003; Daneshvar *et al.* 2006; Huang *et al.* 2011) processes.

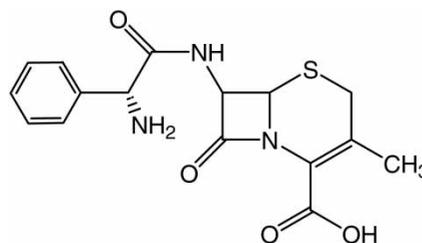
The objectives of the present work are to investigate: (i) the effect of operating parameters on removal of CEX; (ii) the adsorption of cephalexin onto granular activated carbon; (iii) the biodegradability of cephalexin solution; (iv) the optimization of operating conditions using RSM; and (v) the prediction of desired response using ANN. Finally, two responses (chemical oxygen demand (COD) removal and CEX removal) were optimized simultaneously using genetic algorithm (GA) based multiobjective optimization.

## EXPERIMENTAL

### Chemicals and procedure

Granular activated carbon (GAC) was obtained from Effigen Carbon (Malaysia) Sdn Bhd. The size distribution of activated carbon granules was 0.6–2.35 mm. GAC was dried

overnight at 110 °C before use. The single point surface area of GAC was measured using a Thermo Finnigan analyzer (Qsurf series). The instrument temperature was adjusted to 77 K and the sample was degassed for 20 min before analysis. The CEX antibiotic was received from Pharmaniaga Bhd, Malaysia. The chemical structure of CEX is given as:



Ozonation experiments were carried out in a 250 mL stirred glass reactor. A three neck round bottom flask was used as the reactor. Ozone gas was produced using oxygen fed ozone generator (Lab 2B Ozonia). Stock solution of CEX was prepared at an initial concentration of 300 mg/L concentration using deionized water. Working solutions for 100 and 200 mg/L were obtained by dilution of stock solution. Two other working solutions, 24 and 376 mg/L, were prepared fresh before the experimental runs. These concentrations may be higher than the detected concentrations in the water environment (typically in nano- or micrograms per liter). However, it is often difficult to perform experiments with such low concentrations in the laboratory and fairly high concentrations of antibiotics have been used for experimental purposes (Dantas *et al.* 2008; Uslu & Balcioğlu 2009). The pH of solution was adjusted accordingly using 0.1N NaOH or 0.1N acetic acid solution. All experiments were conducted at  $26 \pm 1$  °C. CEX concentration in solution was analyzed on high-performance liquid chromatography (HPLC) (Agilent) using Synergi Hydro-RP (250 mm  $\times$  4.6 mm, 5  $\mu$ m) at 254 nm. The mobile phase was 20 mM ammonium acetate (CH<sub>3</sub>COONH<sub>4</sub>): acetonitrile (CH<sub>3</sub>CN) (75:25 v/v) at a flow rate of 1.5 mL/min. The pH of solution was adjusted to 4.3 using dilute acetic acid. Ammonium acetate solution was filtered using 0.45  $\mu$ m nylon membranes and was mixed with HPLC grade acetonitrile. The size of the injection sample was 10  $\mu$ L. The percentage removal of both CEX and COD was calculated according

to Equations (1) and (2). COD analysis was performed according to the standard Hach method. Biodegradability of solution was measured according to Equation (3).

$$\% \text{CEX removal} = \frac{\text{CEX}_{\text{in}} - \text{CEX}_{\text{out}}}{\text{CEX}_{\text{in}}} \times 100 \quad (1)$$

$$\% \text{COD removal} = \frac{\text{COD}_{\text{in}} - \text{COD}_{\text{out}}}{\text{COD}_{\text{in}}} \times 100 \quad (2)$$

$$\text{Biodegradability} = \frac{\text{BOD}}{\text{COD}} \quad (3)$$

### RSM modeling

A central composite rotatable design (CCRD) is used in the design of experiments (DoE) as CCRD involves fewer experimental runs and gives more reliable information than the normal full factorial design. In CCRD, variance of predicted response rotates around a centre point of design and is a function of distance from the centre (Clarke & Kempson 1997; Montgomery 2001). The values of input variables range from  $-\alpha$  to  $+\alpha$ . Coding of values is necessary for DoE experimental runs. Variables in CCRD are coded as star point ( $-\alpha$ ), minimum ( $-1$ ), centre ( $0$ ), maximum ( $+1$ ) and ( $+\alpha$ ). The values of  $\alpha$  can be calculated according to  $\alpha = (n_c)^{0.25}$ , where  $n_c$  is centre point and is equal to  $2^k$ .  $k$  is the number of independent variables. Three variables were used in our study, so the value of  $\alpha$  is 1.6871. Regression analysis of input and response variables gives a quadratic model that can predict responses as a function of inputs. The general form of the quadratic model is expressed in Equation (4) (Khayet *et al.* 2011). The analysis of variances (ANOVA) was used to determine regression coefficients and effects of interaction terms using Matlab 7.8.0. ANOVA was used to estimate Fisher  $F$ -test values to judge accuracy of the model (Box *et al.* 1978; Clarke & Kempson 1997; Montgomery 2001). For each response,  $t$ -value and  $p$ -value were estimated to assess the significance of the regression model.

$$Y = \beta_0 + \sum_{j=1}^3 \beta_j X_j + \sum_{j=1}^3 \beta_{jj} X_j^2 + \sum_{i < j} \beta_{ij} X_i X_j \quad (4)$$

where  $Y$  is predicted response,  $\beta_0$  = intercept,  $j$  = linear terms,  $jj$  = squared terms,  $ij$  = interaction terms.  $X_j$  and  $X_i$  are uncoded terms.

### ANN modeling

ANN is a useful tool to simulate accurate responses from unorganized input data. ANN is able to solve non-linear complex problems that are difficult in linear computation. In ANN, the individual artificial neuron performs as an independent processor, called a node. The information to each node is adjusted by a weight, called bias. Weight determines variation in output based on changes in input data. Here we used a feed forward multilayer network, called perceptron. Perceptron consists of input, hidden, and output layers. Usually several neurons are present in an input layer. Individual neurons present in the input layer are connected to all of the neurons of the hidden layer via a weight connection. Neurons in the hidden layer connect to the output layer via a similar connection. We used a three-layer back proportion network with tansig (sigmoid) transfer function for hidden layer and purelin (linear) transfer function at an output layer using a Neural Network Toolbox. The Levenberg–Marquardt algorithm (LMA) with back-propagation was used due to its fast convergence rate. The learning rate of 0.5 was selected and other parameters of the network are kept in default value. The experimental data were divided into three sets, i.e. training data (70%), validation data (15%), and test data (15%). After training 100 times, the best network with the best performance for training data, validation data, and test data was obtained. The weights and bias of the best network were recorded. The selected network was used to compare response values.

## RESULTS AND DISCUSSION

### Characterization of GAC

GAC was characterized using Brunauer–Emmet–Teller (BET) analysis. The surface area of GAC was 944 m<sup>2</sup>/g. Microporous and mesoporous volumes of GAC were 0.3217 and 0.1654 cm<sup>3</sup>/g, respectively. Accordingly, GAC has more micropores than mesopores. With such GAC property, one

can expect dominance of surface sorption, since there is little opportunity for any interaction between the bulky CEX molecule and GAC. According to Figure 1, adsorption and desorption curves for  $N_2$  considered for  $0 < P/P_o < 0.5$  reflect the dominance of microporous character at low relative pressure. The hysteresis loop of the  $N_2$ -desorption curve deviated slightly from the  $N_2$ -desorption curve at high  $P/P_o$  values ( $0.5 < P/P_o < 1$ ). The hysteresis loop resembled more the type I of IUPAC classification. The deviation of two curves for  $P/P_o > 0.5$  reflects their resemblance to type IV. Type I informs us about the microporous character of activated carbon while type IV was for mesoporous (Sing 1982). Thus, the GAC used in this study is presumed to be a blend of micropores and mesopores.

### Adsorption of CEX onto GAC

A GAC dose of 1 g/L adsorbed 10% of initial concentration of CEX (200 mg/L). A maximum of 90% of initial concentration of CEX was adsorbed on to GAC for 10 g/L of GAC dose. The low amount of GAC may not be sufficient for adsorbing a large quantity of CEX. However, GAC reflected a very good affinity to adsorb CEX, as is evident in the case of 10 g/L. GAC type catalysts are often helpful to use as catalysts during ozonation (Sagehashi *et al.* 2005; Gu *et al.* 2011). GAC acts as an adsorbent and a catalyst during ozonation reactions. Activated carbon is a proven catalyst for removal of organic compounds from water during ozonation (Sánchez-Polo *et al.* 2005; Beltrán *et al.* 2009; Akhtar *et al.* 2011). Liu *et al.* (2011) reported that GAC (BET 1030  $m^2/g$ ) adsorbed 30 mg/g of CEX at

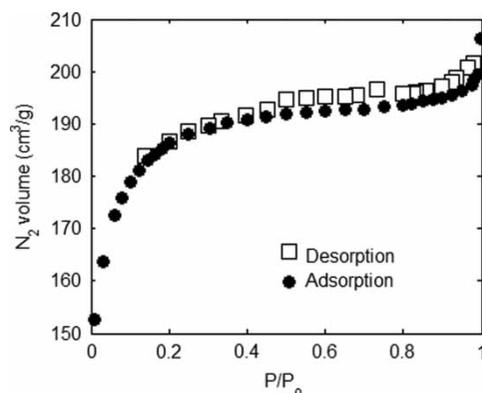


Figure 1 | BET adsorption analysis of GAC.

equilibrium. They also reported the variations in adsorption of CEX as a function of pH of solution. The amount of CEX decreased from 90 to 70% for a change in pH values from 3 to 5. The amount of CEX adsorbed remained stable at 70% for pH 5–10. The significant amount of CEX adsorption onto GAC in Liu *et al.* (2011) and in the present study demonstrates the effectiveness of GAC in adsorbing CEX (Figure 2). Therefore, the effectiveness of GAC is observed for combined adsorption and ozonation of CEX from solution in the next sections.

### Effect of GAC dosage

The GAC dosage exerted influence on removal patterns (Figure 3). All of the experimental curves with GAC catalyst removed more CEX compared to that without GAC catalyst.

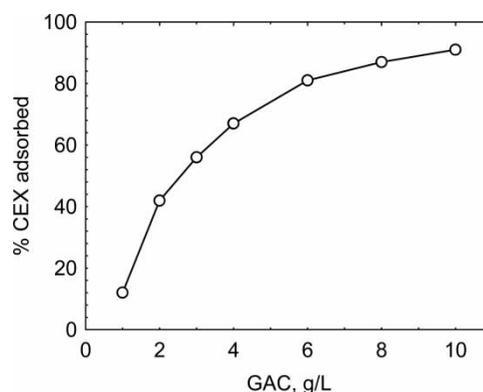


Figure 2 | Effect of GAC dosage on CEX adsorption;  $t = 1$  h,  $26 \pm 1$  °C, 200 mg/L.

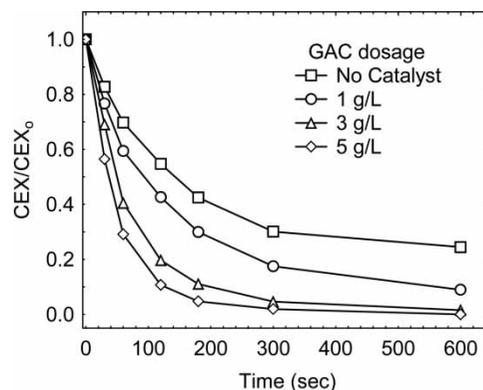


Figure 3 | Effect of pH of solution on removal of CEX concentration. Conditions: CEX concentration 200 mg/L,  $O_3$  dosage 21 mg/L, GAC dosage 4 g/L, temp.  $26 \pm 1$  °C.

This emphasized the importance of GAC catalyst during the ozonation process. The rate of CEX removal increased as a function of GAC dose. The effectiveness of GAC dose followed the order: 5 g/L > 3 g/L > 1 g/L for removal of CEX from solution. GAC doses of 3 and 5 mg/L have supported fast decomposition of CEX and similar behavior. It is clear that a small amount of GAC was necessary for efficient ozonation. Any additional GAC as a catalyst may not be very significant. GAC dosage induced a positive influence on the rate of CEX removal and overall removal of CEX from the solution. Based on this initial study, a GAC dose of 4 g/L was selected for further experiments. All of the experiments hereafter used 4 g/L of GAC. The GAC is important from an adsorption (Álvarez *et al.* 2011) and catalytic (Faria *et al.* 2007) point of view. Due to the high adsorption capacity of activated carbon, a significant amount of CEX is expected to be adsorbed and consequently removed from the solution. The rate of reactions among ozone and CEX particles is normally higher at the surface of activated carbon compared to bulk reactions. Therefore, the addition of GAC exerts a synergistic effect on overall removal of cephalexin. Activated carbon decomposes dissolved ozone and increases the driving force for adsorption of gas phase ozone into water (Pocostales *et al.* 2012). According to Pocostales *et al.* (2012), the absorbable compounds adsorb on the surface of granular activated carbon and at the same time ozone chemisorbs onto the surface as well, where the ozonation reaction takes place. Activated carbon having a large surface area is expected to adsorb more of the absorbable compounds and ozone.

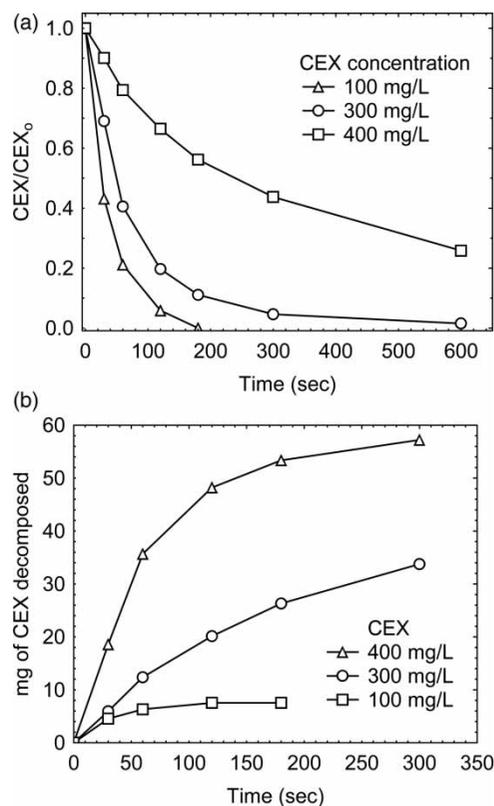
There is competitiveness for the adsorption of any compound and ozone, since adsorption consumes the open pores with the attaching molecules from bulk solution. The chemisorption of ozone onto GAC will face hindrance from already adsorbed organic compounds. The hindrance is minimal in GAC containing large internal pores such as in mesoporous GAC. GAC used in this study, with a surface area of 944 m<sup>2</sup>/g and a mesoporous volume of 0.1654 cm<sup>3</sup>/g, seems to be sufficient for ozonation of CEX and its mineralization (Figure 3).

### Effect of CEX concentration

The concentration exerted negative influence on the removal of CEX using ozonation. The concentrated solution of CEX

took longer to degrade completely. The ozonation took 5 min to remove 100 mg/L of CEX sample from solution and 10 min for 300 mg/L (Figure 4(a)). In general, complete removal of concentrated solutions of antibiotics requires longer ozonation times compared to dilute solutions (Tehrani-Bagha *et al.* 2010). Naddeo *et al.* (2009) observed that 80 mg/L of diclofenac antibiotic solution decomposed in 40 min compared to 20 min for 4 mg/L of solution sample. Arslan-Alaton & Caglayan (2005) observed that 200 mg/L COD solution prepared from penicillin antibiotic was decomposed to 50 mg/L of final COD value in 60 min. Meanwhile 600 mg/L COD solution of the same antibiotic was decomposed to 400 mg/L of final COD value. It is assumed that the initial concentration of antibiotic exerts significant influence during ozonation and that concentrated solutions of antibiotic require more time to decompose.

The above paragraph is the reverse of what is actually observed in Figure 4(b). In fact, removal of CEX increased as a function of initial concentration. As shown in Figure 4(b),



**Figure 4** | CEX removal. (a) Effect of initial concentration, (b) amount of CEX decomposed: GAC dosage 4 g/L, O<sub>3</sub> dosage 21 mg/L, temperature 26 ± 1 °C, pH 7–7.5.

approximately 7 mg of CEX was removed for an initial concentration of 100 mg/L, compared to 27 mg in the case of 300 mg/L and 53 mg in the case of 400 mg/L. The concentrated solutions offset the mass transfer limitations and higher rates of reactions are expected among ozone and CEX reactants. The dilute solutions of CEX acted as a limiting reactant, therefore decreasing the overall rate of reactions. Arslan-Alaton & Caglayan (2005) observed a similar conclusion in that the rate of decomposition of diclofenac solutions decreased at later stages of ozonation. The ozonation reactions are diffusion controlled, and the rate of diffusion of ozone gas into water is much slower than the ozonation reaction itself (Sevimli & Sarikaya 2002). The concentrated solutions of CEX diminish the ozone quickly from the solution and the overall reaction will decrease (Wu *et al.* 1998). Moreover, the concentrated solutions of CEX are likely to produce more secondary by-products. These secondary by-products require a concentrated supply of ozone to mineralize from solution.

### Effect of pH

The effect of pH of solution on removal of CEX is shown in Figure 5. At pH 9, CEX vanished completely within 5 min of ozonation. The complete removal of CEX was observed in the case of pH 7 and approximately 80% of CEX for pH 4.5 in 10 min of ozonation. It is well established that decomposition of substrate increases as a function of pH of solution (Kuo 1999; Ma *et al.* 2005). The ozonation reaction kinetics is defined by the possibility of reactions among substrate and ozone. CEX, which contains sufficient

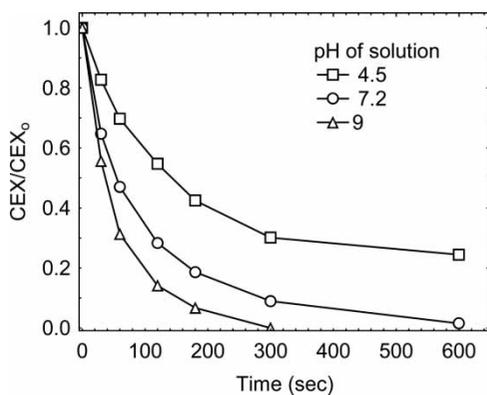


Figure 5 | Effect of GAC dosage on removal of CEX. Conditions: GAC dosage 4 g/L, O<sub>3</sub> dosage 21 mg/L, temperature 26 ± 1 °C, pH 7–7.5.

hot spots for nucleophilic attacks, exhibited a fast reaction rate. The double bond containing CEX structure is more prone to nucleophilic attacks from oxygen and hydroxyl radicals. Assuming pseudo first order kinetics for CEX ozonation for initial 5 min duration, the rate constants for CEX were found to be: 0.0158, 0.0088 and 0.0043 min<sup>-1</sup>, respectively, for pH 9, pH 7, and pH 4.5. According to these rate constants, the pH of solution exerted a significant effect on CEX removal and CEX removal increased with an increase in pH. The high pH of solution induced faster decomposition of dissolved ozone into oxidant radicals (O/OH\*) (Legube & Karpel Vel Leitner 1999). These oxidant radicals possess a high potential for decomposition of organic substrates such as CEX and have the ability to mineralize the secondary by-products. The decomposition of dissolved ozone increases the driving force to transfer ozone from gas to liquid. Therefore, it can be assumed that the increase in decomposition of substrate compound can be attributed to the pH of solution (Andreozzi *et al.* 2006).

### Biodegradability (BOD<sub>5</sub>/COD)

Ozonation processes are known to enhance the biodegradability of potentially refractory substances. Biodegradability can be ascribed as an important characteristic for quality analysis of water samples. Figure 6 shows the effect of GAC assisted ozonation on enhancement in biodegradability of cephalaxin solution. The ratio of biochemical oxygen demand (BOD<sub>5</sub>)/COD increased sharply from 0.1 to 0.4 in just 15 min of ozonation due to the rapid decomposition rate of cephalaxin antibiotic into smaller by-products that

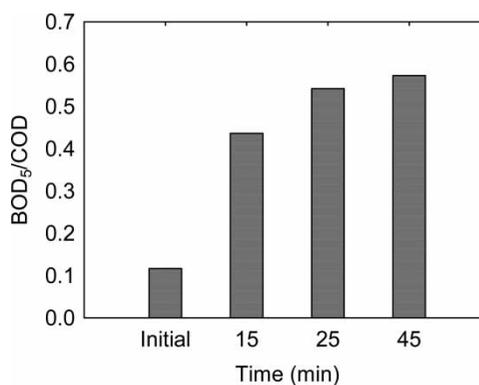


Figure 6 | Increase in biodegradability of CEX solution during ozonation.

possibly are biodegradable. A further increase in ozonation time to 25 or 45 min duration also increased the biodegradability of solution. Overall, BOD<sub>5</sub>/COD increased to 0.58 from 0.11 in 45 min of ozonation, inferring the effectiveness of GAC assisted ozonation on the removal of CEX from solution. It is generally accepted that if the BOD<sub>5</sub>/COD ratio is >0.3, the compounds present in water are readily biodegradable (Ma *et al.* 2005). From this information it can be assumed that simple ozonation of 10–15 min was sufficient for the conversion of refractory CEX into biodegradables. For pretreatment with ozonation purposes, treatment can be employed for a short duration to minimize operational costs and increase the industrial applications of ozonation to treat wastewater (Li *et al.* 2008).

### RSM optimization

Three independent variables, pH of solution ( $X_1$ ), inlet O<sub>3</sub> dosage ( $X_2$ ) and CEX concentration ( $X_3$ ), were chosen due to their significance in catalytic ozonation processes

(Amin *et al.* 2010; Guzman-Perez *et al.* 2011). Ranges of variables were used to investigate from normal to extreme cases of treatment (Table 1). GAC catalyst dosage was fixed at 4 g/L based on initial experiments. It was found that all of the variables influenced overall removal of CEX during catalytic ozonation. The following discussion is based on the experimental results given in Table 2. Removal of CEX increased from 60 to 93% by increasing pH of solution from 2 to 7 (see runs 9 and 10); this emphasizes the importance of pH during ozonation. The concentration of CEX was regarded as a secondary influencing variable. For example, experimental run 14 observed complete removal of CEX at minimum value of CEX concentration (24 mg/L) while run 15 observed 75% removal of CEX at maximum value of CEX concentration (376 mg/L) at the same pH of solution and ozone supply in both runs (see runs 14 and 15). A moderate effect of pH of solution was found on overall removal of CEX. According to runs 1 and 5, a 15% increase in removal of CEX was due to the change in pH from 4 to 10. The ozone supply appeared to

**Table 1** | Coded and uncoded values of input variables and desired response using ANN and RSM

Exp.	Coded values (actual values)			Response		
	pH ( $X_1$ )	O <sub>3</sub> ( $X_2$ ) mg/L	Concentration ( $X_3$ ) mg/L	Observed	Predicted	
					RSM model	ANN model
1	-1 (4)	-1 (16)	-1 (100)	75	69.70	79.34
2	-1 (4)	-1 (16)	+1 (300)	55	52.76	65.13
3	-1 (4)	+1 (35)	-1 (100)	100	101.99	99.11
4	-1 (4)	+1 (35)	+1 (300)	94	90.63	94.66
5	+1 (10)	-1 (16)	-1 (100)	90	88.54	81.18
6	+1 (10)	-1 (16)	+1 (300)	85	77.10	71.99
7	+1 (10)	+1 (35)	-1 (100)	100	96.91	101.30
8	+1 (10)	+1 (35)	+1 (300)	90	91.05	92.58
9	0 (7)	0 (21)	0 (200)	93	94.33	84.54
10	-1.68 (2)	0 (21)	0 (200)	60	62.90	74.60
11	+1.68 (12)	0 (21)	0 (200)	84	88.39	88.22
12	0 (7)	-1.68 (4)	0 (200)	18	20.96	33.11
13	0 (7)	+1.68 (38)	0 (200)	98	98.80	101.40
14	0 (7)	0 (21)	-1.68 (24)	100	101.95	96.47
15	0 (7)	0 (21)	+1.68 (376)	75	79.57	77.03
16	0 (7)	0 (21)	0 (200)	93	94.33	92.6

**Table 2** | The weights and bias of individual variables for ANN model

W1 <sup>a</sup> Neuron	Variables				W2 <sup>c</sup> Neuron	Weight
	X <sub>1</sub>	X <sub>2</sub>	X <sub>3</sub>	Bias		
1	0.1293	-1.3197	-1.9006	3.0016	1	-0.1844
2	1.5023	-1.9394	1.8479	-0.2277	2	-0.4000
3	-0.9938	-1.8033	-0.0871	-1.6441	3	-1.0252
4	-0.8431	1.6752	1.2324	-0.9723	4	0.2692
5	1.3039	-1.6552	-1.2955	1.7063	5	0.3432
6	1.0212	-2.2035	0.1751	2.6085	6	0.0943
					Bias	-0.4166

$r^2 = 0.9259$

be the most influential variable. The concentrated supply of ozone (35 mg/L) made it possible to remove 90–100% of CEX from solution at any value of CEX concentration and pH range (see runs 3, 4, 7, and 8). The effect of CEX or pH was evident only at low concentrations of ozone supply. The inadequate removal of CEX was observed at 4 mg/L of ozone supply. Therefore, removal of CEX was more sensitive to fluctuations in ozone supply compared to the other two variables.

### Quadratic model

Quadratic analysis of experimental data gives the following polynomial (Equation (5)) for removal of CEX.

$$Y = -20.428 + 10.378 \cdot X_1 - 0.527 \cdot X_1^2 + 5.876 \cdot X_2 - 0.083 \cdot X_2^2 - 0.068 \cdot X_3 - 0.0001 \cdot X_3^2 - 0.0761 \cdot X_1 \cdot X_2 - 0.0008 \cdot X_1 \cdot X_3 \quad (5)$$

A plus sign before the term indicates synergetic effects of variables while a negative sign is the indication of an opposed effect (Wu et al. 2010). Both ozone dosage and pH synergized while CEX concentration discouraged the overall removal of CEX. Moreover, removal of CEX depended more on linear terms than quadratic terms, as indicated by large values of coefficients comparatively.

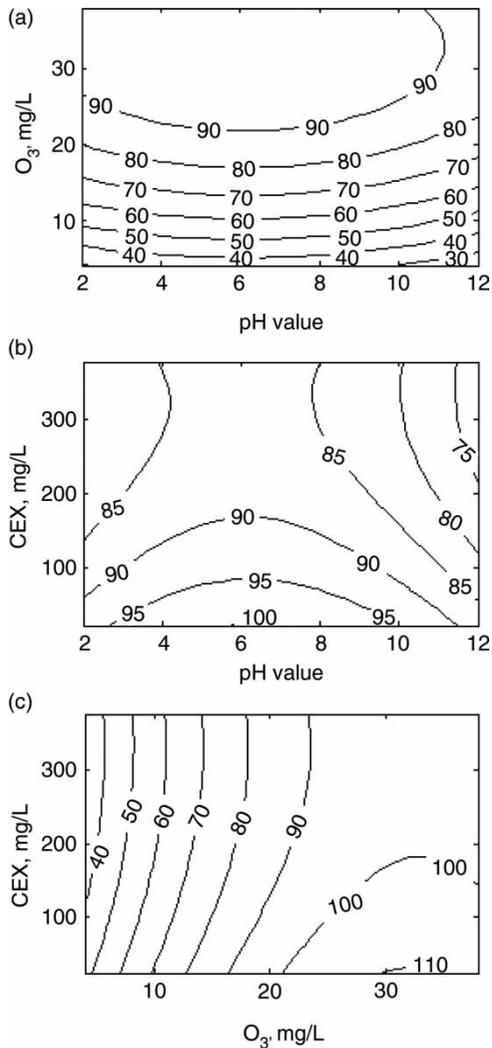
The plot of predicted and experimental responses gave an  $r^2$  value of 0.9521, indicating a reasonable agreement between the two responses. The values of adjusted  $r^2$  (0.9340) also indicated the reliability of the model. This

may represent an adequate model within acceptable error limits. The significance of the regression model was estimated by an  $F$ -value and  $p$ -value test using ANOVA. Usually, a  $p$ -value of  $<0.05$  and an  $F$ -value of  $>0.05$  are set standards for a specific term to be significant at 95% confidence interval (Istadi & Amin 2006). The model had an overall  $p$ -value of 0.03008, suggesting its adequacy for predicting response. Two linear terms ( $X_1$ ,  $X_2$ ), two quadratic terms ( $X_1^2$ ,  $X_2^2$ ), and one interaction term ( $X_{12}$ ) were found to be significant ( $p$ -value  $<0.02$ ). All other terms ( $X_3$ ,  $X_3^2$ ,  $X_{13}$ ,  $X_{23}$ ) were insignificant ( $p$ -value  $>0.05$ ). Based on  $F$ -value and  $p$ -value, the order for significance of variables was  $X_2$  [O<sub>3</sub> dosage]  $> X_2^2$  [O<sub>3</sub> dosage]<sup>2</sup>  $> X_1$  [pH of solution]  $> X_1^2$  [pH of solution]<sup>2</sup>  $> X_{12}$  [pH of solution  $\times$  ozone dosage]. An improved regression model is developed from Equation (5) after eliminating insignificant terms from the model (Equation (6)).

$$\% \text{CEX removal} = -20.428 + 10.378 \cdot X_1 - 0.527 \cdot X_1^2 + 5.876 \cdot X_2 - 0.083 \cdot X_2^2 - 0.0761 \cdot X_1 \cdot X_2 \quad (6)$$

### Contour plots for RSM optimization

Contour graphs illustrating the dependence of CEX removal on input variables are given in Figure 7. Each figure explains the effect of two variables while the value of the third variable was set at centre point. The desired response fluctuated more in the case of O<sub>3</sub> supply as compared to CEX concentration or pH of solution. According to



**Figure 7** | Contour graphs for removal of CEX using RSM optimization.

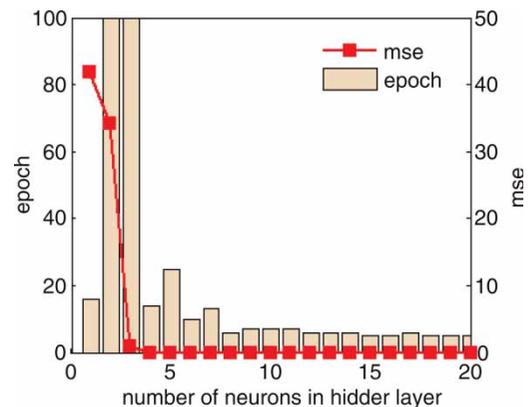
**Figure 7(a)**, an approximately 45% increase in removal of CEX was achieved by increasing the ozone supply from 4 to 28 mg/L. A maximum of 90% CEX is removed from solution at 28 mg/L of ozone supply. One can expect complete removal of CEX for  $O_3$  supplies  $>30$  mg/L (see **Figure 7(a)**). The initial concentration of CEX exerted a slight influence on its removal from solution (see **Figure 7(b)**). The removal of CEX varied from 80 to 95% by changing the pH of the solution from 2 to 12. It is shown in **Figure 7(b)** that the CEX concentration exerted an agonistic effect on CEX removal and that CEX removal decreased by approximately 10% by increasing initial concentration of CEX from 100 to 200 mg/L.

According to **Figure 7(c)**, removal of CEX sharply reached 100% as  $O_3$  supply increased from 5 to  $>20$  mg/L. However, CEX was not removed completely from a very concentrated solution of CEX ( $>210$  mg/L), even at very high  $O_3$  supply ( $>35$  mg/L), as shown by the saddle point in **Figure 7(c)**. This saddle point reflects that the excessive supply of ozone was not able to decompose concentrated CEX solution. The explanation for such behavior may be the diffusion limit of ozone dissolution in water. Due to low solubility of ozone it is quite possible that excessive ozone gas may not be able to dissolve in water and bubble out of water in the exhaust gas (Akhtar *et al.* 2011). The optimum value of  $O_3$  supply might be 30 mg/L for the concentration of CEX between 150 and 180 mg/L at centre point values of pH of solution (pH 7). The removal of CEX was above 100% in a few of the optimized values shown in **Figure 7(c)**. This may be ignored because it is quite possible for response surface methodology to reach more than 100% conversion (Tugba 2009; Sadri Moghaddam *et al.* 2010; Hasan *et al.* 2011; Chatterjee *et al.* 2012).

### Optimization using ANN

#### Optimization of neuron nodes

The first step was to optimize neurons in the hidden layer. A minimum value of mean square error (MSE) for prediction and training was the criterion to select the optimum number of neurons (Yetilmezsoy & Demirel 2008; Elmolla *et al.* 2010). **Figure 8** illustrates the correlation between



**Figure 8** | Optimization of neurons and epoch for CEX removal.

MSE and neurons for the Levenberg–Marquardt algorithm. MSE was more than 25 for one neuron in the hidden layer as an initial guess. MSE decreased to 0.005 when six neurons were used in the hidden layer. A significant decrease in epoch level was also observed. There was a slight decrease in epoch level, but MSE did not change for the higher number of neurons for neuron numbers from six to 20 in the hidden layer. Six neurons were selected as the optimum number of neurons. The ANN model used is a three layer structure containing sigmoid transfer function (tansig) at the hidden layer and linear transfer function (purline) at output.

### Relative importance of parameters

Table 2 shows the weights for input and response variables. Weights are coefficients of artificial neurons for hidden or output layer and represent relative contributions of neurons to response variables. Each weight is the proportion of an individual signal transmitted to the neuron (Kuo et al. 2002). These individual weights are helpful to calculate the relative importance of each variable for output response. The relative importance of variables was estimated using Garson's equation, which is based on partitioning of connection weights (see Equation 5 in Elmolla et al. 2010).

Table 3 tabulates the relative contribution of each variable to removal of CEX during ozonation. The O<sub>3</sub> supply contributed almost half (50%) of the total effect on response variables, followed by pH of solution (28.84%) and concentration of CEX in solution (20.43%). The relative importance order  $X_2 > X_1 > X_3$  is similar to the conclusions obtained in regression or ANN models. The contribution of all three parameters is significant (>20% at least).

The ozone supply is the measure of sufficiency of oxidant species to attach to pollutant CEX. As the ozone supply increases, the probability of direct and indirect reactions increases and hence, the overall removal of the pollutant compound. The pH of solution is an additive

factor during ozonation. The pH of solution enhances ozone utilization by inducing decomposition of dissolved ozone (Lin et al. 2009). It is a secondary factor and its effectiveness depends upon the initial supply of O<sub>3</sub>. The influence of initial concentration of CEX was minimal and also agonistic. The concentrated solutions of CEX required more ozone supply to decompose.

### Contour plots for ANN optimization

The optimum values of O<sub>3</sub> supply, CEX concentration, and pH observed from the ANN model were similar to those observed in RSM, i.e. 30 mg/L of O<sub>3</sub> supply, 6–8 pH of solution and 200–210 mg/L of initial CEX concentration. As shown in Figure 9(a), a 70% increase in removal of CEX

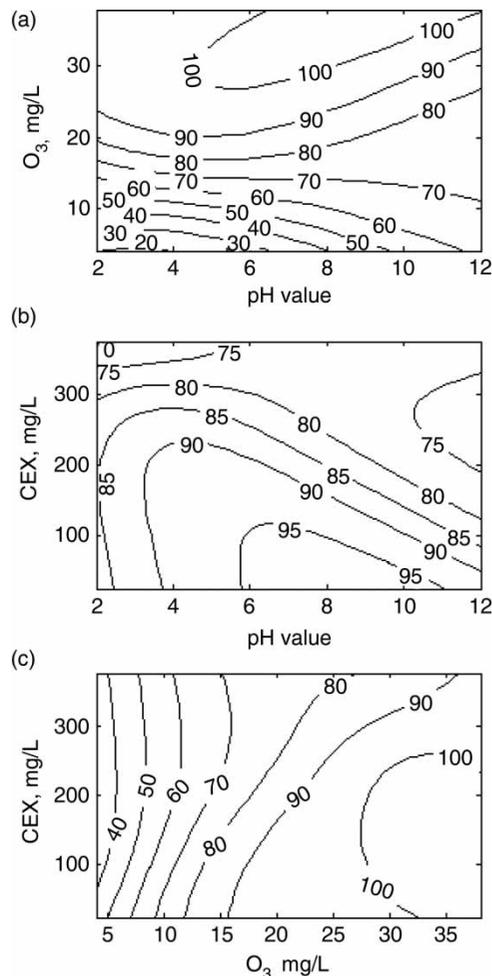


Figure 9 | Contour graphs for removal of CEX using ANN optimization.

Table 3 | Relative influence of three variables on output response

Response	Relative importance of variables (%)			Total
	pH	O <sub>3</sub> dose mg/L	CEX dose mg/L	
Y (CEX removal, %)	28.84	50.73	20.43	100.00

was observed by changing the O<sub>3</sub> supply from 5 to 30 mg/L. Similarly, a 30% increase in the removal of CEX was observed by increasing the pH of solution from 2 to 12. Figure 9(a) reflects the O<sub>3</sub> supply as the dominantly influencing variable and pH exerted significant influence. The concentrated O<sub>3</sub> supply was expected to transfer more ozone from gas to liquid and could destroy CEX from solution at faster rates. The pH of solution decomposed dissolved ozone into radical oxidants and thereby induced the destruction of CEX from solution. Figure 9(b) represents the interaction effect of pH of solution and concentration of CEX. Approximately 20% of the variation in removal of CEX is attributed to the interaction of CEX and pH of solution. At the centre point value of O<sub>3</sub> supply (21 mg/L), a maximum of 95% of CEX was removed, which indicates that complete removal is only possible at high O<sub>3</sub> supply. Interaction of O<sub>3</sub> supply and CEX concentration produced about 60% variation in output response, as shown in Figure 9(c). The optimum region is the contour lines describing 100% removal of CEX shown in Figure 9(c).

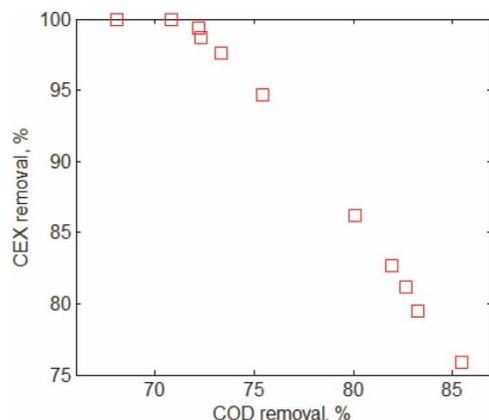
Figure 9 explains the dominant effect of O<sub>3</sub> supply followed by pH of solution and concentration of CEX on removal of CEX from solution. The dominance of O<sub>3</sub> supply is due to its reactive nature, which aggressively attacks double bonds in organic compounds (Razumovskii & Zaikov 1980). Therefore, overall removal of an organic compound will mainly depend on the amount of ozone supply in the ozonation processes (Konsowa 2003). The pH of solution is a supporting variable that influences overall removal by decomposing dissolved ozone. Decomposition of dissolved ozone leads to better ozone utilization and generation of reactive oxidant species (O, OH) (Morooka *et al.* 1988). The pH of solution, therefore, has an indirect influence on overall removal. With the use of GAC, the effect of pH will be even smaller because GAC also decomposes dissolved ozone (Sánchez-Polo *et al.* 2005). Nevertheless, an increase in pH of solution facilitated the removal of CEX from solution. The concentration of CEX, on the other hand, suppressed overall removal from solution. A concentrated solution of CEX required more O<sub>3</sub> supply and long exposure. Overall, contours developed by the ANN model gave precise estimation about the influence of input variables on removal of CEX from solution.

### Multiobjective optimization for removal of CEX and COD

The influence of input variables was simultaneously observed for two responses, i.e. CEX removal and COD removal. In multiobjective optimization, multiple solutions are possible and are called Pareto optimal solutions. Pareto optimal solutions are a non-dominated set of solutions. The Pareto front scans the objective functions for the identification of non-dominated solutions. Scanning of objective functions allows the capture of promising solutions from a random population and analyzing those solutions for optimized solutions. By scanning, the Pareto front carefully characterizes objectives to a common solution and trades off confronting variables. The Matlab (R2009a) optimization toolbox was used to generate the Pareto front for the said responses by the 'gamultiobj' function. The RSM equation models developed for two responses were optimized simultaneously using 'gamultiobj' function. Minimum and maximum ranges of three input variables were selected as lower and upper bounds.

Population type:	Double vector
Population size:	45
Crossover fraction:	0.8
Crossover function ratio:	1
Migration direction:	Forward
Migration fraction:	0.2
Generation stopping criteria:	600 generations weighted average

The optimized Pareto front was achieved after 200 iterations and is given in Figure 10. Each point in optimal front corresponds to an optimized solution. Table 4 gives a list of decision variables corresponding to each Pareto optimal solution. Localized optimum solutions are given in Figure 10 for the removal of CEX and COD. Optimized values of COD and CEX removal varied on a narrow range of input variables. Careful analysis of Table 4 indicates that for complete removal of CEX, the optimized values of COD ranged from 65 to 72%. With this information, 72% can be regarded as the maximum value of COD that can be removed at optimum conditions, i.e. 9.7, 34.5, and 33.6 for pH of solution, O<sub>3</sub> concentration, and CEX concentration, respectively.



**Figure 10** | A set of Pareto optimal solutions for removal of COD and CEX obtained by GA multiobjective optimization.

**Table 4** | The Pareto optimal solutions and corresponding values of input variables

Runs	pH	Input variables		Responses	
		Ozone concentration mg L <sup>-1</sup>	CEX concentration mg L <sup>-1</sup>	COD removal %	CEX removal %
1	11.99	37.54	30.82	85.45	75.88
2	11.76	37.02	33.81	83.24	79.50
3	11.48	37.29	32.49	82.68	81.14
4	9.20	32.51	33.99	68.08	100
5	11.49	35.24	32.77	80.06	86.23
6	9.56	35.28	35.97	72.30	98.70
7	9.75	35.34	34.23	73.33	97.57
8	9.70	34.49	33.63	72.18	99.40
9	10.44	34.77	32.26	75.44	94.67
10	11.48	36.73	32.52	81.94	82.64
11	10.44	30.92	34.37	70.80	100

## CONCLUSIONS

All three parameters influenced the removal of CEX during ozonation according to the following order: ozone supply (50%) > pH of solution > (30%) > CEX concentration (20%). Ozone supply and pH of solution exerted a synergistic effect, while that of CEX concentration was agonistic. The biodegradability of solution was enhanced in that BOD<sub>5</sub>/COD increased to 0.58 after 45 min of ozonation. The best ANN network using the Levenberg–Marquardt back propagation optimized the complete

removal of CEX for 30 mg/L of O<sub>3</sub> supply, pH 6 and 150 mg/L of CEX concentration within 95% confidence interval. Simultaneous optimization of two responses (COD removal and CEX removal) was performed using genetic algorithm based multiobjective optimization. The optimum value obtained from multiobjective optimization was 100% removal of CEX and 72% removal of COD. The corresponding input variables for optimized multiobjective solutions were 9.7, 34.5, and 33.6 for pH of solution, O<sub>3</sub> concentration, and CEX concentration, respectively.

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