

Multi-objective optimization of ciprofloxacin antibiotic removal from an aqueous phase with grey taguchi method

M. Salari, G. R. Rakhshandehroo and M. R. Nikoo

ABSTRACT

Optimization methods are used to study and survey the optimal values for input factors and effect of optimized parameters on response variables. In this study, the effect of different factors on ciprofloxacin (CIP) removal of water soluble was studied. In this regard, a multi-objective optimization was performed utilizing the Taguchi method based on a grey relational analysis. Optimum levels of factors were determined to optimize three responses simultaneously with grey Taguchi. Meanwhile, grey relational analysis was applied to model and optimize three target responses, namely, CIP removal, chemical oxygen demand (COD) removal, and sludge to iron ratio. Multi-objective optimization results obtained based on grey relational analysis showed that the optimal value of the input factors were CIP concentration of 100 mg/L, H₂O₂ concentration of 100 mM, Fe(II) concentration of 10 mM, pH of 3, and a reaction time of 15 min. To confirm the results, the values obtained through a confirmation test were examined. Multi-objective optimization results from process factors were determined by analysis of variance (ANOVA) analysis and grey Taguchi method. Based on ANOVA analysis for the grey relational grade, Fe(II) concentration and H₂O₂ concentration were found to be the most influencing factors.

Key words | ciprofloxacin, grey relational analysis, homogeneous Fenton process, multi-objective optimization, Taguchi method

M. Salari
G. R. Rakhshandehroo (corresponding author)
M. R. Nikoo
Department of Civil and Environmental
Engineering,
Shiraz University,
Shiraz,
Iran
E-mail: rakhshan@shirazu.ac.ir

INTRODUCTION

Global presence of pharmaceutical products in drinking water supplies and wastewater effluents has raised concerns regarding its potential effects on aquatic life, human health, and antibacterial resistance (Ludmilla *et al.* 2010; Haddad & Kümmerer 2014; Verlicchi & Zambello 2015). With a limited number of sources of drinking water and increasing population growth, it is necessary to ensure that drinking water is available, abundant, and safe for future generations (Zhang *et al.* 2015). Generally, pharmaceutical antibiotics can be highly hazardous to the environment and humans, if over-used or misused. It is believed that a considerable proportion of antibiotics reach water and soil environments, since many antibiotics are not completely metabolized or eliminated in the body (Watkinson *et al.* 2007; Cho *et al.* 2014).

Ciprofloxacin (CIP) is a broad-spectrum fluoroquinolone (FQs) antimicrobial antibiotic and can be used for

both human and animal illnesses. These compounds have a low environmental degradation and a toxic effect on environmental bacteria has been recorded (Vasconcelos *et al.* 2009). This statement implies that there is a high risk for exposed environmental compartments, making it necessary to employ a treatment process that can eliminate remaining CIP compounds (Vasconcelos *et al.* 2009; Rakhshandehroo *et al.* 2017).

Advanced oxidation processes (AOPs) are recommended for wastewater constituents (such as pesticides or pharmaceuticals) that have high chemical stability and/or low environmental degradation. Considering the ability of AOPs to achieve a complete mineralization of pollutants to CO₂, water, and inorganic compounds, or at least their partial oxidation to more biodegradable or less harmful intermediates, AOPs demonstrate an even more useful and

cost-efficient ability when combined with biological processes (Pereira *et al.* 2011; Cho *et al.* 2014). Most previous studies have only regarded the relationship between performance of the method and processing factors and have not addressed the combination factor in a multi-objective optimization of the responses. Therefore, this study focuses on a multi-objective optimization approach based on the grey Taguchi method.

Generally, experimental factors are set by empirical rules or trial and error method, which can be time-consuming and uneconomical. On the other hand, the Taguchi experimental design method only conducts optimization of a single quality response (Kuo *et al.* 2011). Such studies have already been conducted utilizing the Taguchi method to optimize the Fenton process and electro-oxidation for removal of many organic contaminants from an aqueous phase (Asghari *et al.* 2012; Nandhini *et al.* 2014; Dehghani *et al.* 2016).

The Taguchi method makes it possible to optimize the parameters to achieve optimal response by minimizing number of experiments, reducing costs, and providing robust solutions (Taguchi 1987, 1993).

However, when the response factors are more than one, the Taguchi method for optimization may give a different set of optimal levels for each response. Therefore, for more than one quality response, a multiple quality analysis method is required. In general, the grey Taguchi method is a highly effective and accurate approach because it emphasizes multiple responses or objectives. Today, many researchers have utilized this approach to analyze multiple quality response problems for different areas (Chen *et al.* 2000; Tarnig *et al.* 2002; Chiang & Hsieh 2009; Sarikaya & Gullu 2015; Pahange & Abolbashari 2016; Shinde & Pawar 2017). However, we have not seen any published research studying the application of this approach to environmental contaminants, and particularly CIP antibiotic. The main objectives of this research are to perform a multi-objective optimization of CIP antibiotic removal from an aqueous phase with the grey Taguchi method. In this regard, an optimized combination of processing factor levels was determined based on the Taguchi method and grey relational analysis. The Taguchi method was adopted for experimental planning, and 16 experiments were conducted using L_{16} orthogonal array, while maintaining the robustness of experiments.

It is worth noting that in previous studies, most researchers concentrated on evaluating AOPs for degradation of antibiotics using the Taguchi method for one or two responses independently. For example, Rasoulifard *et al.* (2015) showed that the optimized conditions for removal of cefixime trihydrate from aqueous solution in the presence of peroxydisulfate by the Taguchi method were observed at a temperature of 50 °C, current intensity of 1,800 mA, drug concentration of 10 ppm, peroxydisulfate concentration of 120 mM, for a time of 30 min. Finally, cefixime trihydrate degradation 91.79% was realized in optimum conditions. Dehghani *et al.* (2016) evaluated the optimal conditions for the removal of amoxicillin in the aqueous phase by the Taguchi method. The results at optimum conditions showed that the maximum removal efficiency of chemical oxygen demand (COD) and mineralization rate was 71.3% and 36.3%, respectively. In these conditions, optimum values of parameters including the initial amoxicillin concentration, Fe(II) concentration, H_2O_2 concentration, pH and reaction time were observed as 500 mg/L, 5.0 mg/L, 500 mg/L, 3 and 15 minutes, respectively. Also, Kurt & Yonar (2017) investigated optimal condition AOPs for treatability of hospital wastewaters containing antibiotics by the Taguchi method. The obtained results for the Fenton processes showed that COD and total organic carbon (TOC) removal rates were 91.8% and 70.8%, respectively. The recommended optimum conditions were pH 4, with 25 mg/L H_2O_2 and 75 mg/L $FeSO_4$ after 30 min. Recently, Jafarzadeh *et al.* (2018) evaluated the degradation of metronidazole (MNZ) and optimization with Taguchi approach from aqueous solutions by using GO/ β -CD/Ag nanocomposite. In this research, the effect of parameters such as pH solution (2–5), adsorbent dosages (0.2–1 g/L), contact time (10–80 min), initial MNZ concentrations (0.25–10 mg/L), and ionic strength (0.001–0.1 mol/L) were investigated. The obtained results show that optimum values of contact time, initial MNZ concentration, ionic strength, adsorbent dosage, and pH solution were 20 min, 0.25 ppm, 0.01 mol/L, 0.4 g/L, and 2, respectively. To the best of our knowledge, a multi-objective optimization homogeneous Fenton process by Taguchi method and grey relational analysis to remove CIP antibiotic from an aqueous phase with three responses simultaneously has not been studied.

METHODS

Chemical and reagents

In this study, analytical grade reagents were utilized in all experiments. CIP (98%) was purchased from a local provider, Temad Pharmaceutical Company, and distilled water was used as a solvent to prepare all solutions. Ferrous sulfate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$), sulfuric acid (H_2SO_4 (95–70%)), sodium hydroxide (NaOH), and hydrogen peroxide (H_2O_2 (30%)) were all obtained from Merck, Germany.

The standard solution

The pharmaceutical antibacterial CIP, used to treat infections caused by bacteria, is an important contributor to the contamination of wastewaters (PubMed 2011). Stock solution of 500 mg/L was prepared every week by dissolving CIP in distilled water and was kept at 4 °C. The chemical structure of CIP is shown in Figure S1 (available with the online version of this paper).

The overall structure of this research consists of three main steps: step 1: Taguchi's design of experiments (DOE); step 2: execution of the experiments, data collection, and examination; and step 3: multi-objective optimization of the process. A flowchart for the proposed methodologies to optimize CIP antibiotic removal based on the grey Taguchi method is presented in Figure 1.

Homogeneous Fenton process

In recent years, AOPs have been used to reduce pollution caused by the presence of pharmaceutical residues in water, without discharging any secondary toxic contaminants to the environment (Garoma *et al.* 2010). Fenton is an advanced oxidation process, first discovered in 1890. Fenton reaction initiates with the addition of both iron and hydrogen peroxide to remove various contaminants (Wang *et al.* 2010). Significant advantages of the Fenton method include high efficiency, biodegradability enhancement, simplicity in operation, and flexibility. In the conventional Fenton process, H_2O_2 and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ are employed as an oxidant and a catalyst, respectively,

enabling it to treat refractory wastewaters to organic compound at room temperature (Alver *et al.* 2015). For each experiment, after setting the antibiotic concentrations, the initial pH solutions were adjusted with the addition of NaOH and H_2SO_4 (1 M) and considered until the reaction time was completed. Measurements of pH solutions were done using a WTW (340i; WTW, Germany, pH meter).

Design of experiments

DOE is a statistical method and powerful technique for process optimization that is used to reduce the number of experiment cases within possible limits. In this method, optimal conditions can be used to determine the desired experimental responses with several influential factors and their interactions (Liao 2006). Levels chosen for independent factors in this study (A to E) for the coded experiments (1 to 4) are shown in Table 1. The range of these parameters was selected according to literature and preliminary experiments (Ma *et al.* 2015; Gupta & Anurag 2018).

Taguchi orthogonal array

Taguchi design was applied to obtain maximum information with a minimum number of experiments based on an orthogonal array. Moreover, it was utilized to analyze the experimental data based on signal-to-noise (S/N) ratio and the analysis of variance (ANOVA) (Ross 1996). Taguchi's method to design experiments is simple. It eliminates the need for repeated experiments, saving time and material, and allowing users with limited knowledge of statistics to implement the method. Taguchi orthogonal array (OA) design is a type of general fractional factorial design (Taguchi 1987, 1993; Karna *et al.* 2012). In this study, multi-objective optimization including removal of CIP, removal of COD and sludge to iron ratio (SIR) is performed using the homogenous Fenton process, based on the grey Taguchi method. CIP removal percentages ($\text{Re}\%$) were determined using Equation (1):

$$\text{Re}\% = \left(1 - \frac{C_f}{C_0}\right) \times 100 \quad (1)$$

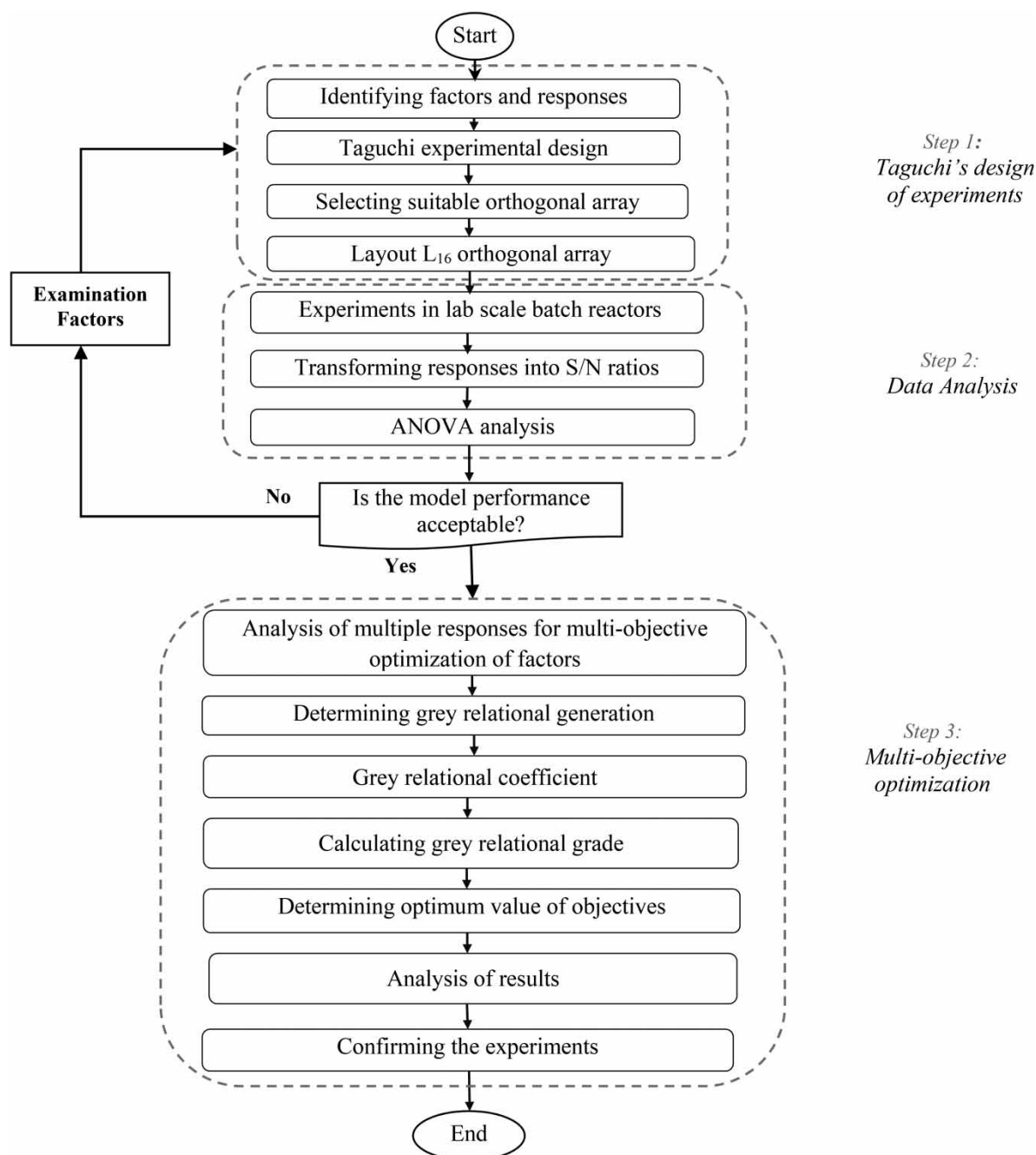


Figure 1 | Proposed methodology for multi-objective optimization of CIP antibiotic removal based on grey Taguchi method.

where C_0 and C_f are initial and final concentrations of CIP in the solution at the corresponding wavelengths λ_{\max} , respectively.

COD measurements were performed using a COD reactor and direct readings by a spectrophotometer (DR/5000, HACH, USA), according to the standard

method. For this, COD test cells supplied by Merck were heated in a thermo-reactor (Spectroquant DR 200), after adding the required amount of the sample. Subsequently, absorption measurements were carried out in a spectrophotometer according to the standard method, and COD removal efficiency was

Table 1 | Factors and their levels in the Taguchi design with homogenous Fenton process

Factor	Description	Coded experiments ^a			
		1	2	3	4
A	Concentration of CIP (mg/L)	10	50	100	200
B	Concentration of hydrogen peroxide (mM)	10	20	50	100
C	Concentration of ferrous ions (mM)	5	10	25	50
D	Time (min)	10	15	20	30
E	pH	2	3	4	5

^aLevel (1–4) means different levels for each factor.

calculated:

$$\text{Removal of COD(\%)} = \left(1 - \frac{\text{COD}_f}{\text{COD}_0}\right) \times 100 \quad (2)$$

where COD_0 and COD_f are initial and final CODs of the solution, respectively (WEF & APHA 2005).

In this study, a response called SIR is adopted due to its comprehensive concept (Amiri & Sabour 2014; Biglarijoo et al. 2016, 2017).

$$\text{Sludge to iron ratio (SIR)} = \frac{\text{Produced sludge volume (gr)}}{\text{Added ferrous iron (gr)}} \quad (3)$$

The overall strategy for the responses of CIP and COD removal was the-larger-the-better, and for SIR it was the-smaller-the-better, which may be mathematically defined as follows (Jun et al. 2005; Liu et al. 2009):

(a) Larger-the-better/Higher-the-better

$$S/N = -10 \log_{10} \left(\frac{1}{n} \sum_{i=1}^n \frac{1}{y_i^2} \right) \quad (4)$$

(b) Smaller-the-better/Lower-the-better

$$S/N = -10 \log_{10} \left(\frac{1}{n} \sum_{i=1}^n y_i^2 \right) \quad (5)$$

where y_i and n are the observed response value and the total number of measurements, respectively. After experimental

planning, experiments were performed to obtain experimental data from a combination of various orthogonal factors in an orthogonal array, and a response graph was generated. To minimize the required experimental effort, Taguchi's L_{16} orthogonal array was performed, and the corresponding results are shown in Table 2. The Taguchi method was used to optimize factors and their levels via MINITAB[®] software. Higher CIP and COD removal rates and lower SIRs were considered as targets.

Multi-objective optimization using grey Taguchi

The grey Taguchi approach is a progressive form of the Taguchi method, which emphasizes the optimization of more than one output factor, rather than optimizing a single one (Kuo & Su 2003, 2007). The Taguchi method considers a set of different numbers for the input factors; it may consider an L_{16} or L_9 orthogonal array depending upon the degree of accuracy desired. Taguchi design, as described by Antony (2001) and Ross (1996), has found a larger use than any other conventional method. The stages of the grey Taguchi approach are as follows (Kuo & Su 2003, 2007).

Step 1: Grey relational analysis is utilized to convert a multiple-response optimization problem into one with a single response (Julong 1982, 1989). This method provides approaches for analysis and modeling of systems for which the information is limited, imperfect, and/or ambiguous. This objective function in the grey relational analysis should be normalized, as well as the generation of grey relations applied to the empirical data related to the responses; the results are used to obtain grey relational grades (GRGs) to rank each series of data.

Basically, grey relational analysis is widely applied to processes with multiple responses to find the optimum factor (Julong 1989). The fundamental idea is to assign a certain grey grade to every factor. To apply this method, S/N ratios of response factors may be normalized in the range of 0 to 1. If the response is 'the-larger-the-better', then the original runs may be normalized as:

$$x_i(k) = \frac{x_i^{(0)}(k) - \min x_i^{(0)}(k)}{\max x_i^{(0)}(k) - \min x_i^{(0)}(k)} \quad (6)$$

Table 2 | Experimental results of L_{16} for control factors and output responses

RN	CIP (mg/L)	H ₂ O ₂ (mM)	Fe(II) (mM)	Time (min)	pH	CIP removal (%)	COD removal (%)	SIR ^a (gr/gr)
1	10	10	5	10	2	80	24	0.6
2	10	20	10	15	3	86	36	0.8
3	10	50	25	20	4	83	25	0.96
4	10	100	50	30	5	82	27	1.03
5	50	10	10	20	5	76.5	31	0.6
6	50	20	5	30	4	77	45	0.71
7	50	50	50	10	3	78	34	0.76
8	50	100	25	15	2	81.5	35	0.62
9	100	10	25	30	3	78	48	0.8
10	100	20	50	20	2	71	44	0.81
11	100	50	5	15	5	70	49	0.52
12	100	100	10	10	4	73	38	0.85
13	200	10	50	15	4	64.5	53	1.2
14	200	20	25	10	5	55	52	0.8
15	200	50	10	30	2	68	49	0.75
16	200	100	5	20	3	72	43	0.55

^aSIR: Sludge to iron ratio.

Similarly, if the purpose is ‘the-smaller-the-better’, then the original runs may be normalized as:

$$x_i(k) = \frac{\max x_i^{(0)}(k) - x_i^{(0)}(k)}{\max x_i^{(0)}(k) - \min x_i^{(0)}(k)} \quad (7)$$

where $x_i(k)$ is the grey relational generated value, $\min \cdot x_i^{(0)}(k)$ and $\max \cdot x_i^{(0)}(k)$ are the smallest and largest value of $x_i^{(0)}(k)$, respectively, for the k^{th} response.

Step 2: Grey relational coefficient is calculated to express the relationship between the optimal (best = 1) and actual normalized results (Das *et al.* 2014). The grey relational coefficient $\xi_i(p)$ may be calculated using Equation (8):

$$\xi_i(p) = \frac{\Delta_{\min} + \psi \Delta_{\max}}{\Delta_{0i(p)} + \psi \Delta_{\max}} \quad (8)$$

$\Delta_{0j} = \|y_0(p) - y_j(p)\|$ = The absolute value of the difference between $y_{0(k)}$ and $y_{i(k)}$

$\Delta_{\min} = \min_{\forall j \in J} \|y_0(p) - y_j(p)\|$ = The smallest value of $y_{j(k)}$

$\Delta_{\max} = \max_{\forall j \in J} \|y_0(p) - y_j(p)\|$ = The largest value of $y_{j(k)}$

ψ is the distinguishing coefficient $0 \leq \psi \leq 1$; 0.5 is the value used in most situations (Yang & Huang 2012; Rajmohan *et al.* 2013; Pandey & Panda 2014; Yeh & Tsai 2014). A higher grey relational coefficient implies that the corresponding experimental result is closer to the optimal (best) normalized value for a single response (Pandey & Panda 2014; Sarikaya & Gullu 2015; Pahange & Abolbashari 2016; Roy *et al.* 2016).

Step 3: Once the grey relational coefficients are determined, the overall grey relational grade is calculated using Equation (9). Generally, the higher the value of grey relational grade, the greater the desirability (Yeh & Tsai 2014):

$$\delta_i = \sum_{p=1}^n w_p \xi_i(p) \quad n = 1, 2, 3 \quad (9)$$

where n is the number of output responses, w_p is the weighting value for each grey relational coefficient, p , ranging from 0 to 1 with its sum being equal to 1. In the present study, equal w 's ($w_1 = w_2 = w_3 = 0.33$) were assigned as weighting factors for the response variables of CIP removal, COD removal, and SIR, respectively.

RESULTS

Analysis of S/N ratio

As mentioned earlier, S/N ratio represents the ratio of a desirable to an undesirable value for output responses. The S/N ratios for CIP removal, COD removal, and SIR using the homogenous Fenton process are shown in Tables S1 to S3 and Figures S2 to S4, respectively (available with the online version of this paper). As shown in Table S1, the highest S/N ratios are observed at level 1 for factor A, at level 2 for factors C and E, and at level 4 for factors B and D. Furthermore, factor A has the highest and factor C the lowest range of variations (delta and rank), respectively. Figure S2 shows the main effect plots for factors A to E (all on the same scale) in CIP removal obtained by MINITAB® software.

As shown in Table S2, response values of S/N ratio for COD removal are slightly different than those for CIP removal. Here, the highest S/N ratios are observed at level 4 for factor A, at level 2 for factors B, D, and E, and at level 1 for factor C. However, similar to the case of CIP

removal, factor A has the highest and C the lowest rank, with the highest and lowest range of variations (delta and rank), respectively. Figure S3 shows the main effect plots for factors A to E in COD removal obtained by MINITAB® software. As shown, the plots are slightly different to the plots for CIP removal, generally having a wider range of variations for the factors.

Based on the results of S/N ratios for SIR (Table S3), the highest ratios are observed at level 1 for Factors C and E, at level 2 for factor A and E, and at level 3 for factors B and D. Factor C has the highest and factor B the lowest rank. Obviously, experiments may be optimally performed at levels with the highest S/N ratios. Figure S4 shows the main effect plots for factors A to E in SIR obtained by MINITAB® software. As shown, the trend in the plots is very different to previous plots, reflecting the very different nature of the SIR process compared to CIP or COD removal.

S/N and its normalized ratio for responses are both presented in Table 3. As shown, runs number 14, 1, and 13 have the lowest S/N ratios (and zero normalized S/N) for CIP removal, COD removal, and SIR, respectively. These values may be converted into grey scale coefficients, where

Table 3 | Signal-to-noise (S/N) ratio and normalized S/N ratio for conducted experiment

Run	CIP removal		COD removal		SIR	
	S/N ratio	Normalized (S/N)	S/N ratio	Normalized (S/N)	S/N ratio	Normalized (S/N)
1	38.06	0.838	27.60	0.000	4.44	0.829
2	38.69	1.000	31.13	0.524	1.94	0.485
3	38.38	0.921	27.96	0.053	0.35	0.267
4	37.62	0.893	28.63	0.152	−0.26	0.183
5	37.67	0.738	29.83	0.331	4.44	0.829
6	37.73	0.753	33.06	0.813	2.97	0.628
7	38.22	0.782	30.63	0.450	2.38	0.546
8	37.84	0.880	30.88	0.488	4.15	0.790
9	37.62	0.782	33.62	0.896	1.94	0.485
10	37.21	0.618	32.87	0.784	1.83	0.470
11	36.90	0.539	33.80	0.923	5.68	0.470
12	37.27	0.633	31.60	0.594	1.41	1.000
13	36.19	0.356	34.49	1.025	−1.58	0.000
14	33.80	0.000	34.32	1.000	1.94	0.485
15	35.27	0.475	33.80	0.923	2.50	0.485
16	36.65	0.602	32.67	0.754	5.19	0.933

the higher grey relational grade will indicate a better multi-response quality.

Grey relational coefficients with grey relational grade for each performance response are shown in Table 4. As shown, experimental run 12 scores the highest grey relational grade and, consequently, may be considered as the best experimental setup to provide the best strategy for obtaining the optimal solution and satisfying the set multiple objectives, simultaneously. Generally, higher grey grades indicate closer to the optimal responses in the process.

Mean grey relational grades (GRG) at each level are shown in Table S4 for all factors. GRG values are represented graphically in Figure 2. They are calculated by taking the average for each level group for process factors. Since they denote the level of correlation between reference sequence and obtained sequence, higher values for mean GRG indicate stronger correlations between them. The highest value indicates optimal level for the process factors.

As shown in Figure 2, the highest GRG is observed at level 3 for factor A. However, it occurs at level 4 for factor B and at level 2 for factor C, D, and E. Overall, factor C

has the highest, and factor D the lowest rank, meaning that the former has the best multiple performance quality (with a composition closest to the optimal point) and the latter has the worst. According to the graph (Figure 2), the best combination of multi-objectives to meet all three targets simultaneously is $A_3B_4C_2D_2E_2$.

Figure 3 shows the GRG for all experiments. The results demonstrate that the experimental run 12 has the maximum value of GRG. In other words, the 12th experiment gives the best multi-performance characteristics among all experiments.

DISCUSSION

The ANOVA test for GRG is a statistical technique for analyzing the effect of design factors on responses. The results of ANOVA on the GRG values are shown in Table 5. Results indicate that concentration of CIP, concentration of ferrous ions, concentration of hydrogen peroxide, time, and pH all influence GRG values, by 19.14%, 20.34%, 38.23%, 5.37%, and 16.89%, respectively. Therefore, Fe(II) concentration and H_2O_2 concentration are identified as the two factors that significantly affect GRG values, and on the other hand time has less effect on GRG values.

Confirmation test

Once the most influential factor is identified in the grey Taguchi method, the final phase would be to verify optimization results and to determine the improvement of responses. For this purpose, GRG at the optimal level of the design factors may be estimated as (Yeh & Tsai 2014):

$$\gamma_c = \gamma_m + \sum_{i=1}^q (\gamma_i - \gamma_m) \quad (10)$$

where γ_c , γ_m , γ_i , and q are the estimated GRG, the total average GRG, the average GRG at the optimal level, and the number of design factors, respectively (five here).

Estimated GRGs and experimental values obtained from simulation at the optimum point are indicated in Table 6. Generally, this table indicates that there is a

Table 4 | Grey relational coefficients with grey relational grades

Grey relational coefficients

Run	CIP removal	COD removal	SIR	Grey relational grades	Rank
1	0.756	0.333	0.745	0.605	9
2	1.000	0.513	0.493	0.662	4
3	0.863	0.345	0.405	0.533	15
4	0.824	0.371	0.380	0.520	16
5	0.656	0.428	0.745	0.604	10
6	0.669	0.728	0.573	0.650	6
7	0.696	0.476	0.524	0.560	14
8	0.806	0.494	0.704	0.661	5
9	0.696	0.828	0.493	0.666	3
10	0.567	0.698	0.485	0.578	13
11	0.521	0.867	0.485	0.618	7
12	0.577	0.552	1.000	0.703	1
13	0.437	1.052	0.333	0.601	12
14	0.333	1.000	0.493	0.603	11
15	0.488	0.867	0.493	0.609	8
16	0.557	0.670	0.882	0.696	2

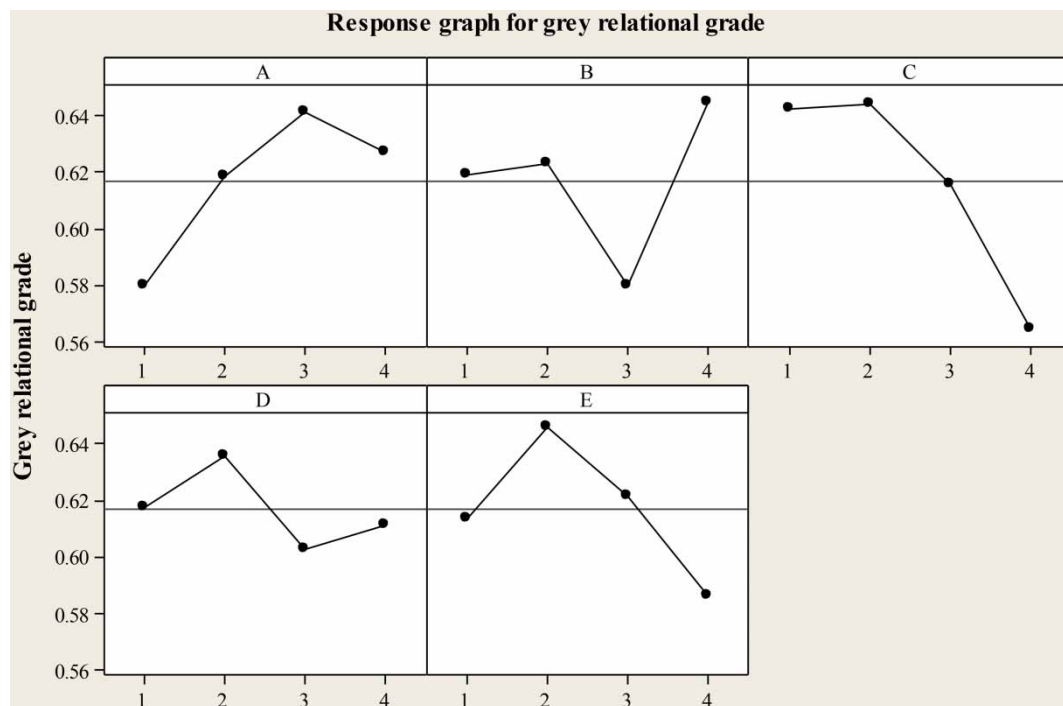


Figure 2 | Response graph for mean grey relational grade (GRG) of parameters.

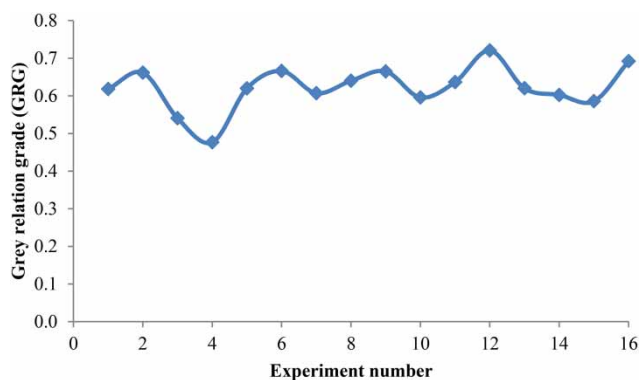


Figure 3 | Comparison of grey relational grades (GRGs) for all experiments.

good agreement between the predicted and experimental results.

The predicted value obtained by GRG is 0.8253, while the response values at the optimal setting from confirmation experiments are 78% for CIP removal, 53% for COD removal, and 0.8 for SIR, with a GRG value of 0.8041. One may conclude that GRG value is validated, as evidenced by an improvement of 2.63% in the confirmation experiment as compared to the predicted mean value.

CONCLUSIONS

In this research, application of the Taguchi method and a grey relational analysis based multi-objective optimization was performed for the removal of CIP antibiotic from an aqueous phase. An attempt was made to explore the effect of CIP concentration (mg/L), ferrous ions concentration (mM), hydrogen peroxide concentration (mM), time (min), and pH on CIP and COD removals and SIR when a minimum number of experiments are desired. To reduce the experimental effort, Taguchi's L_{16} orthogonal array was used to design the experiments. A combination of grey relational analysis with Taguchi was also suggested for performance optimization.

The following conclusions may be drawn based on the above analysis:

- (1) Multi-objective optimization results obtained using grey relational analysis shows that the optimal combination of the input factors are CIP concentration of 100 mg/L, H_2O_2 concentration of 100 mM, Fe(II) concentration of 10 mM, pH of 3, and a reaction time of 15 min.

Table 5 | ANOVA for overall grey relational grades

Factors	Degree of freedom	Sum of squares	Adjusted mean squares	F value	Percentage of contribution
Concentration of CIP (mg/L)	3	0.00826	0.00275	0.95	19.14
Concentration of hydrogen peroxide (mM)	3	0.00878	0.00293	1.02	20.34
Concentration of ferrous ions (mM)	3	0.01650	0.00550	2.48	38.23
Time (min)	3	0.00232	0.00077	0.23	5.37
Initial pH	3	0.00729	0.00243	0.81	16.89
Error	12	0.03437	–	–	–
Total	15	0.04315	–	–	–

Table 6 | Results of confirmation test for verifying the result of grey relational grade

Factor	Optimal	
	Prediction	Experiment
Response	$A_3B_4C_2D_2E_2$	$A_3B_4C_2D_2E_2$
CIP removal (%)		78
COD removal (%)		53
SIR (gr/mol)		0.8
Grey relational grade	0.8253	0.8041
$Error = \frac{Prediction - Experiment}{Experiment} \times 100\% = 2.63\%$		

- (2) Based on the ANOVA for the GRG, Fe(II) concentration and H_2O_2 concentration with contributions of 38.23% and 20.34%, respectively, were found to be the most influential factors for the chosen objectives of the highest CIP and COD removals, and the lowest SIR.
- (3) The results of the confirmatory test showed that there is a significant progress in the multi-performance index GRG for experimental values. The Taguchi-based grey approach is an appropriate one to create the best possible solution for the set of input process variables, depending on the desired multi-performance characteristics.
- (4) The largest max–min value was explored in the response table in CIP and COD removals. It is found that CIP concentration is the most significant factor among all involved process factors.
- (5) Results demonstrate that the 12th experimental run has the maximum GRG value. Thus, the 12th experiment gives the best multi-performance characteristics among all experiments.
- (6) The GRG value improves by 2.63% (compared to the predicted mean value) in the confirmation experiment; an improvement that confirms experimental validity.

Comparison of the results of this study with those of previously conducted research (Rasoulifard *et al.* 2015; Dehghani *et al.* 2016; Kurt & Yonar 2017; Jafarzadeh *et al.* 2018) indicates that the efficiency of the process was improved by utilizing the grey Taguchi method for multi-objective optimization of multiple responses.

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