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Integration of ozonation with water treatment for pharmaceuticals removal from Arroio Diluvio in southern Brazil

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ABSTRACT

Pharmaceutical compounds can reach water bodies through sewage systems. The process of water treatment is insufficient for the removal of these contaminants. The ozonation has great potential to be integrated into the treatment, since it promotes the reduction of pharmaceuticals, reduces the generation of disinfection byproducts and can reduce operational costs. In this work, the integration of the ozonation process with water treatment was studied. The ozone was applied in the pre-oxidation and intermediate ozonation stages, to evaluate the dependence of different variables. Water samples were collected from Arroio Diluvio, a river of the city of Porto Alegre (Brazil). The doses of ozone were maintained between 0.5 and 1.0 $mgO_3\ L^{-1}$ while the coagulant was between 25 and 150 $mg·L^{-1}$. Pre-ozonation resulted in a removal of pharmaceuticals at pH 10.0, time of 15 min and coagulant concentration of 52.5 mgL^{-1}. The intermediate ozonation provided a removal with pH 10.0 and a time of 5 min of bubbling. Based on the results, it was confirmed that the synergy of the ozonation process with conventional water treatment is an effective, sensitive and fast method for the removal of pharmaceuticals from the aqueous medium.

Key words: advanced oxidative processes, experiment planning, ozonation, water treatment

HIGHLIGHTS

- The water treatment is insufficient for the removal of drugs.
- The adverse effects of drugs in water are still unknown.
- The Arroio Dilúvio, a stream, flows into the Guaíba River, which is used as a source of supply for the treatment of water in the city.
- Ozonation is effective for drug removal and mineralization.
- Ozonation provides a reduction in the amount of reagents used to regulate pH and for coagulation.

GRAPHICAL ABSTRACT
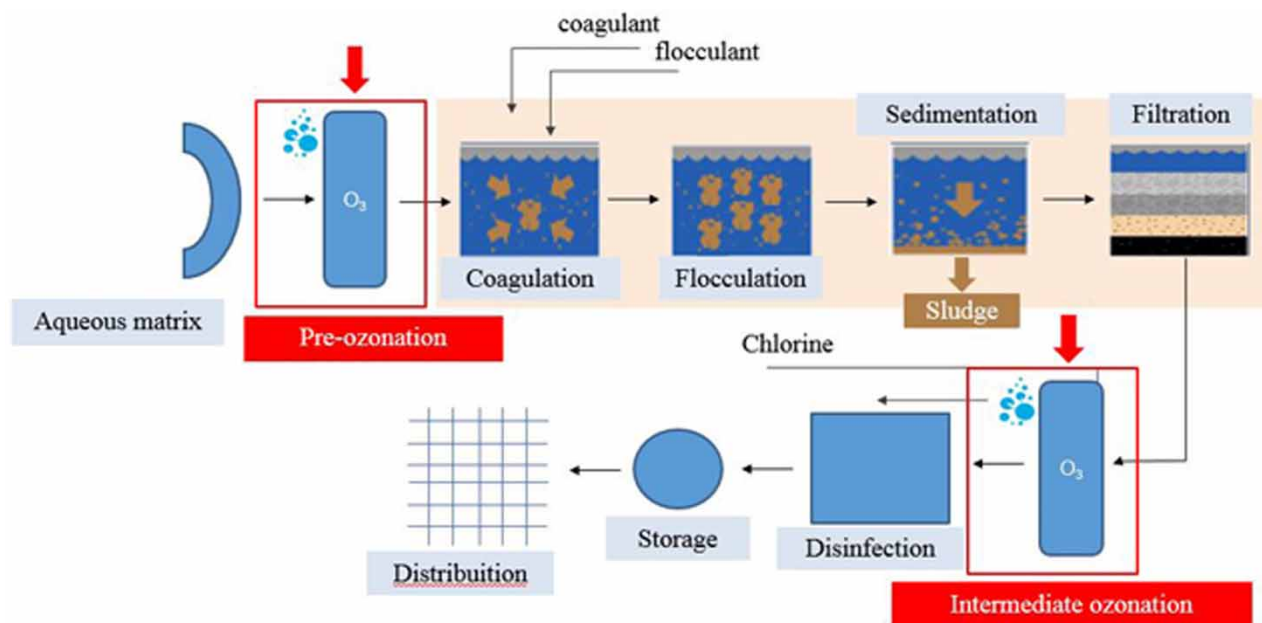
1. INTRODUCTION

The use of pharmaceutical compounds in human and veterinary medicine is a generalized therapeutic approach. Currently, these compounds are constantly being found in the environment and, even at low concentrations ($\mu g \cdot L^{-1}$ and $ng \cdot L^{-1}$), present some concern, since they are considered unregulated compounds and their impacts are still poorly understood (Zapparoli *et al.* 2011; Petrie *et al.* 2015; Yao *et al.* 2017; Bisognin *et al.* 2018; Huang *et al.* 2019; Ramírez-Malule *et al.* 2020; Rigueto *et al.* 2020; Vargas-Berrones *et al.* 2020).

Several causes are involved in the appearance of drugs in environmental matrices. Overuse, misuse and incomplete therapeutic treatments are the main factors generally related to this increase (O'Flaherty *et al.* 2017). Another can be eliminated via excretion, in the unmodified form (original drug) and as metabolites, which can be converted into other transformation products, both by metabolism and by degradation processes (Kümmerer *et al.* 2016; Zhang *et al.* 2016).

Many authors have reported the presence of caffeine (CAF) and ampicillin (AMP) in urban wastewater, surface and groundwater and the biological activity of these antibiotics in the environment (Potrich 2014; Haro 2017; Arsand *et al.* 2020, 2018; Montoya-Rodríguez *et al.* 2020; Bachmann *et al.* 2021). Caffeine, in addition to its pharmaceutical relevance as a diuretic compound and cardiac, brain and respiratory stimulant (Paíga & Delerue-Matos 2017), is an alkaloid present in more than 60 plant species and also an important ingredient in a wide variety of food and beverages (Rigueto *et al.* 2020). Ampicillin (AMP) is considered a β-lactam antibiotic, indicated for the treatment of urinary, oral, respiratory, digestive and biliary tract infections. In addition, it is also indicated for the treatment of local or systemic infections caused by certain germs (Haro 2017; Rosset *et al.* 2020).

Brazil represents one of the main pharmaceutical markets in the world (Tannoury & Attieh 2017; Arsand *et al.* 2020). Furthermore, only about 40% of the sewage generated in this country is treated (von Sperling 2016), confirming the possibility of the presence of drugs in these matrices (Prichula *et al.* 2016). In the southern region of the country, for example, the presence of pharmaceutical compounds was detected in Arroio Diluvio, a stream that cuts through the city of Porto Alegre – RS, in concentrations that reach 93.7 $ng \cdot L^{-1}$ (Jank *et al.* 2014). As it crosses the urban area of the city, this stream receives in nature both domestic effluents as well as some industrial and hospital effluents (Arsand *et al.* 2018, 2020). It is worth mentioning that it flows into the Guaiba River, which is used as a source of supply for the treatment of water in the city.

Given all this, it is clear that the removal of drugs from aqueous matrices is a matter of concern. As an aggravating factor, water treatments based on physicochemical processes present some limitations for the complete removal of pollutants of this

type. In most of them, removal is only partial, decreasing with the alkalinity of the raw water and increasing with the concentration of total organic carbon in the influent (Rosa *et al.* 2009; Yao *et al.* 2018).

Alternatively, the ozonation process has been used in order to adapt treated water to restrictive disinfection standards, reduce the generation of disinfection byproducts (DBPs) from chlorine and pesticides, meet the organoleptic demand for taste, odor and color and, in some cases, reduce the operational cost of treatment (Araújo 2021). It has already been proven that this process promotes the reduction of emerging pollutants such as pharmaceuticals (Naddeo *et al.* 2015; Nie *et al.* 2015; Yargeau & Danylo 2015; Guo *et al.* 2016, 2015; Barik & Gogate 2017; Chandak *et al.* 2020). Countries such as France, the United States, the Netherlands and Japan have already adopted this treatment method. However, in Brazil, there are still no reports on the use of ozone in water treatment plants (Beniwal *et al.* 2018; Bu *et al.* 2019; Mansouri *et al.* 2019).

In this context, the focus of the present work was to study the integration of the ozonation technique into the conventional process of water treatment of Arroio Dilúvio, in Porto Alegre-RS, aiming to evaluate possible benefits in the removal of the compounds CAF and AMP and in the optimization of the operational parameters.

2. EXPERIMENTAL METHODOLOGY

2.1. Treatment proposal

Since conventional water treatments, based on physicochemical processes, present a certain limitation for the complete removal of drugs, it is proposed in this work, the inclusion of ozonation in the conventional process, in pre-ozonation and intermediate ozonation stages, in order to promote the reduction of caffeine and ampicillin drugs from the Arroio Diluvio stream, located in southern Brazil. Figure 1 shows a flowchart of the process proposed in the present study in relation to water treatment in Brazil, including ozonation in the two mentioned stages.

The proposed change consists of the addition of a pre-ozonation step, applied before the coagulation and flocculation processes, which can reduce the amount of reagents used to favor the precipitation of metallic cations, removal of color, odor and flavor and cell rupture of bacteria and other microorganisms. Furthermore, even at low gas dosages, this step can improve the biodegradability of the matrix, since ozonation leads to low molar mass compounds, aldehydes and carboxylic acids (Gerrity & Snyder 2011; Verlicchi *et al.* 2015). Intermediate ozonation acts as a form of matrix polishing, after the physicochemical processes, being responsible for both the degradation and mineralization of organic compounds, as well as for disinfection (Oneby *et al.* 2010).

At the Brazilian level, the proposal is considered promising, since there are no reports in the literature on the use of ozone in water treatment plants in the country, including the southern region (Beniwal *et al.* 2018; Bu *et al.* 2019; Mansouri *et al.* 2019). In addition, it can be said that the inclusion of ozonation in the system would bring benefits compared to the process
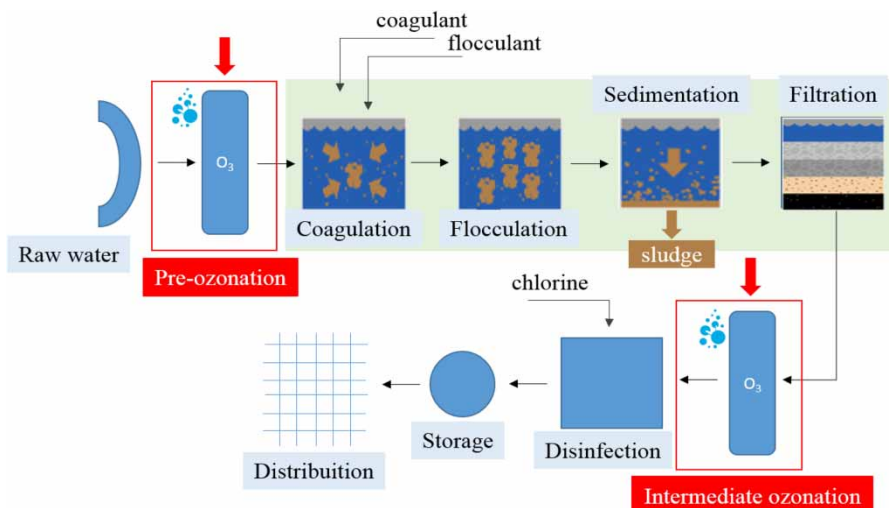
Figure 1 | Flowchart of a water treatment process in Brazil with the inclusion of pre-ozonation and intermediate ozonation steps.

already carried out, since, from an operational point of view, these processes can be applied with high efficiencies, helping to enhance the current treatment (Pills Report 2012).

2.2. Sampling and pre-treatment procedure

Water samples were collected near the Arroio Diluvio Ecobarrier, located in the municipality of Porto Alegre – RS (30°02′50.7″South and 51°13′49.4″West), Brazil (Figure 2). Its small extension passes through a region of great urbanization and high discharge of industrial, hospital and domestic effluents in nature, making this stream an adequate system to evaluate the presence of the proposed compounds.

Sampling was performed in drums with a volumetric capacity of 5 L, which were previously cleaned and sterilized. After this procedure, the drums were transported to the analysis site, filtered to remove particulate material, using a cellulose membrane filter with a pore size of 14 μm and, finally, kept under refrigeration at 4 °C $\pm$ 2. In order to increase the efficiency of the raw water treatment process, after filtration, a preliminary study was carried out to evaluate the best pH condition and the best concentration of the aluminum sulfate coagulant (PA, Synth) and the flocculant Mafloc 2880A (Masterquimica) for the reduction of colloidal substances.

The initial characterization of the matrix before and after the filtration and preliminary treatment is shown in Table 1.

2.3. Sample preparation for antibiotic quantification

For the identification of CAF and AMP in surface water, samples were prepared using the solid phase extraction technique (EFS), using cartridges containing reversed polymeric phase (Strata-X, Phenomenex) and a Manifold system (Supelco). Methods were determined/adapted from existing methodologies (Ruela *et al.* 2005; Jank *et al.* 2014; Arsand *et al.* 2018; Costa *et al.* 2020).

2.4. Detection and quantification in high-performance liquid chromatography

The analyte detection and quantification system consisted of a high-performance liquid chromatography (HPLC) (model 1200 Infinity, Agilent). The chromatographic separation was performed at 35 °C, on a C18 analytical column (5 μm, 250 × 4.6 mm) (Phenomenex); DAD detector at 205 and 273 nm. A binary mobile phase was used with a flow rate of 1 mL·min^{-1} in a total run of 15 min. Mobile phase component A was ultra pure water (70%) and component B was methanol (30%). The isocratic
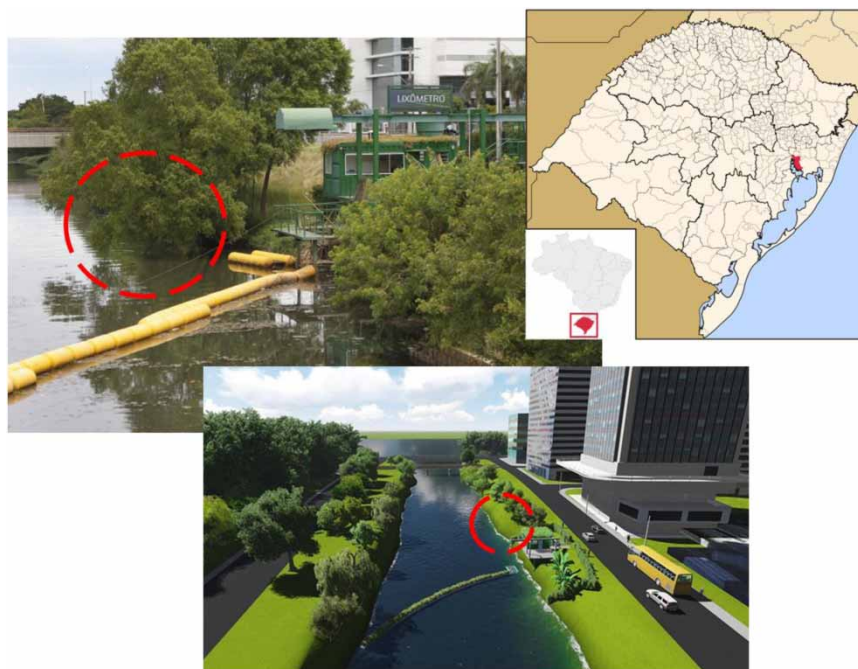
Figure 2 | Sampling point at the Arroio Diluvio Ecobarrier, Porto Alegre – RS (30°02′50.7″South and 51°13′49.4″West), Brazil.

Table 1 | Initial characterization of the aqueous matrix

Parameter[a]	Aqueous matrix	
	Before preliminary treatment	After preliminary treatment
Temperature	23.5	23.5
pH	7.5	7.3
Color (mgPt-CO L^{-1})	36.0	10.0
Turbidity (UT)	7.9	1.0
Conductivity (µS)	420.0	418.0
Alkalinity (mg·L^{-1} of CaCO3)	225.7	182.3
CAFO (mg·L^{-1})	5.8	5.0
AMPO (mg·L^{-1})	33.1	30.1
TOCO (mgC L^{-1})	40.8	36.8

[a]Analytical methods followed the standards of the Standard Methods for the Examination of Water and Wastewater (APHA 2017).

elution mode and integration by the height parameter of the peaks obtained in the chromatograms were adopted. The sample injection volume was 35 µL.

2.5. Statistical design of experiments

Experimental design is generally suitable for simultaneously optimizing the effect of variables to increase efficiency attributes and reduce errors with the fewest possible number of runs (Adio *et al.* 2017). The Central Composite Design (CCD) as a widely suitable optimization method allows the approximation of the coefficients in a mathematical form and predicts the reaction and the validation of the method (De Carvalho *et al.* 2016).

In this study, different CCDs were applied for the percentage of CAF and AMP removal. For the pre-ozonation assays (Table 2), a planning was carried out with 3 factors (pH (x_1), time (x_2) and coagulant concentration (x_3)) in 5 levels, contemplating 16 runs with duplicate at the central point. In the intermediate ozonation tests (Table 3), a planning with 2 factors (pH (x_1) and time (x_2)) was carried out in 5 levels, contemplating 10 runs with duplicate at the central point. In both processes, the ozone flows were fixed at low (0.5 L·min^{-1}) and high (1 L·min^{-1}). The terms R%$_{CAF}$ and R%$_{AMP}$ refer, respectively, to the response variable of the percentage of removal of the drugs caffeine and ampicillin. The software used for planning and processing the results was STATISTICA 10.0. Central points were used to measure data reproducibility and experimental error.

Tables 2 and 3 illustrate the points of the experimental design with the coded values of the variables used in the experiment matrix.

The following second-order polynomial model (Equation (1)) can be used to approximate the mathematical relationship between the independent variables (Tehrani & Zare-Dorabei 2016).

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \sum_{j=1}^{k} \beta_{ij} x_i x_j + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \varepsilon \tag{1}$$

where Y refers to the predicted response (the percentage of CAF and AMP removal) while β_{ij} shows the interaction coefficient, β_{ii} represents the quadratic, β_i shows the linear coefficient and β_0 is the constant coefficient. Furthermore, x_i and x_j represent the independent variables, and ε and k, respectively, refer to the residual error and the number of independent variables.

The design was performed randomly to reduce the effect of uncontrolled variables. Furthermore, this design has the ability to approximate the quadratic effects and the main interaction. RSM was used to allow considerable specification and evaluation of the relative factors and solve the multivariate equation to acquire an optimal response. The modeling was performed by fitting the first- or second-order polynomial equations to the experimental reactions. Subsequently, the acquired results were investigated by analysis of variance (ANOVA) to specify the essential effects of the variables and their interactions. Three-dimensional graph plotting was performed to generate the surface response used to predict optimal operating conditions based on the F-value and p-value.

Table 2 | Experimental design matrix and responses (RSM) for pre-ozonation

Independent variables	Level							
	−1.68 (−α)	Low (−1)	Center (0)	High (+1)	+1.68 (+α)			
x_1: pH	4	6	8	10	–			
x_2: time (min)	1	5	10	15	30			
x_3: coagulant concentration (mg·L^{-1})	75	67.5	60	52.5	45			
				R%$_{CAF}$	R%$_{AMP}$	R%$_{CAF}$	R%$_{AMP}$	

	Independent variables			Flow rate (L min^{-1})				
Run order	x_1	x_2	x_3	Low (0.5)		High (1)		
1	−1	−1	−1	67.3	38.0	97.1	72.8	
8	+1	+1	+1	92.4	84.0	99.5	86.7	
9	−α	0	0	66.9	52.7	98.7	75.1	
5	+1	−1	−1	38.7	48.2	96.2	68.3	
13	0	0	−α	72.2	51.4	96.2	70.0	
18 (C)	0	0	0	75.3	57.3	99.5	77.6	
16 (C)	0	0	0	69.4	60.6	94.2	75.6	
12	0	+α	0	82.2	61.7	99.5	61.0	
3	−1	+1	−1	83.6	63.8	97.1	81.9	
7	+1	+1	−1	89.9	61.2	97.0	89.2	
11	0	−α	0	50.0	22.4	96.0	77.2	
6	+1	−1	+1	19.4	38.7	96.2	79.0	
2	−1	−1	+1	36.1	40.1	97.5	84.0	
4	−1	+1	+1	89.0	75.7	97.0	77.0	
10	+α	0	0	64.9	77.0	98.9	88.0	
17 (C)	0	0	0	70.3	56.9	99.5	70.5	
14	0	0	+α	40.7	48.1	98.9	75.4	
15 (C)	0	0	0	67.5	55.4	96.5	73.1	

2.6. Ozonation procedure

2.6.1. Description of the pilot system

The aqueous matrix was ozonated using an ozonation pilot (Figure 3) comprising an ozone generator device from pure oxygen (DegradaTox/AquaOz, model 3.0E), medical oxygen cylinder (>99.9%, Oxisul, Brazil), a liquid/gas contact column (Vidrolab, Brazil), 500 mL washer flasks, portable pump (for recirculation of water in the column).

The transfer of ozone to the liquid mass was performed in the classic bubble column with a volume of 200 mL, injecting the gas through a porous diffuser, located at the base of the gas inlet tube. The excess gas, that is, the portion of the gaseous mixture that was not retained in the liquid mass, exited through the top of the column and was sent to the washing flasks. The ozone concentration was determined by the iodometric method, in which the volume of the gas was diverted to a flask containing potassium iodide.

2.6.2. Pre-ozonation tests

In the stage of pre-ozonation studies, raw water was ozonized for further conventional treatment. In this experiment, 100 mL of the raw water sample was placed in the glass column and, in the gas washer flask, 120 mL of 2% KI solution was added per test. After ozonation, an aliquot of the ozonated sample was collected to read the pH parameter, and the remainder of the ozonized sample was directed to the physicochemical treatment (FQ) step, where the sulfate coagulant was added to the ozonized water of aluminum and the flocculant Mafloc, according to the experimental design specifications (item 2.4, Table 2).

Table 3 | Experimental design matrix and responses (RSM) for intermediate ozonation

Independent variables	Level				
	−1.41 (−α)	Low (−1)	Center (0)	High (+1)	+1.41 (+α)
x_1: pH	4	6	8	10	−
x_2: time (min)	1	5	10	15	30

Run order	Independent variables		Flow rate (L min^{-1})			
	x_1	x_2	Low (0.5) R%$_{CAF}$	Low (0.5) R%$_{AMP}$	High (1) R%$_{CAF}$	High (1) R%$_{AMP}$
1	−1	−1	91.9	97.3	99.3	98.2
9 (C)	0	0	88.4	98.7	99.5	98.7
4	+1	+1	94.5	97.5	99.5	98.6
2	−1	+1	90.2	97.3	99.4	98.3
10 (C)	0	0	90.6	98.1	99.6	98.8
6	+α	0	88.4	96.3	99.2	98.4
3	+1	−1	98.2	97.4	99.3	98.2
7	0	−α	95.8	97.3	99.3	98.1
5	−α	0	85.7	94.4	99.1	97.5
11 (C)	0	0	86.6	97.2	99.3	98.0
8	0	+α	94.5	90.3	98.5	95.9
12 (C)	0	0	90.0	97.4	99.4	98.4
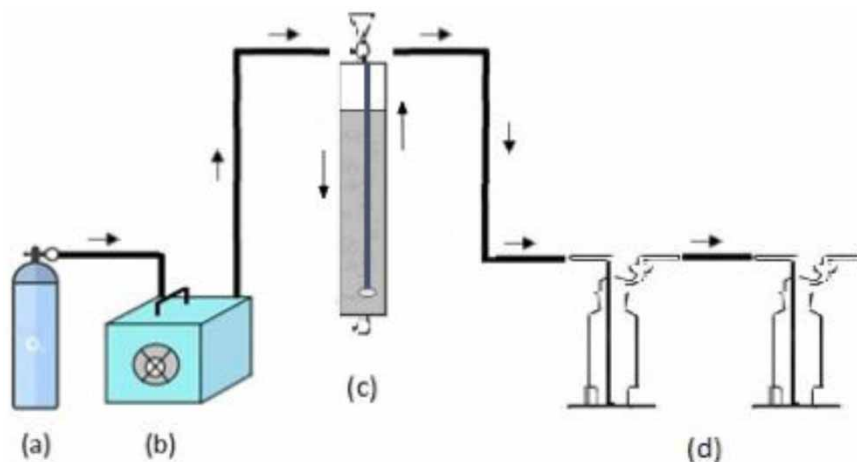
Figure 3 | Representative schematic of the ozonation system: (a) medical oxygen cylinder, (b) ozone generator, (c) glass column with porous stone diffuser and (d) washer flasks containing KI (off-gas).

At the end of the FQ, the sample was filtered through a cellulose membrane filter with a pore size of 0.20 μm and later sent for analysis in HPLC. The application of the ozonation process isolated from the raw water sample was called PO, while the integration of pre-ozonation and the physicochemical treatment was called POFQ, with the collection of the supernatant after sedimentation.

2.6.3. Intermediate ozonation tests

In the FQ tests for intermediate ozonation, a concentration of 75 mg·L^{-1} of aluminum sulfate, 3 mg·L^{-1} of Mafloc and the natural pH of the samples (approximately 7.4) was used, a condition established with the results of the preliminary tests

of physical–chemical treatment. After the FQ, 100 mL of the clarified sample was placed in the glass column and in the gas washer bottle, 120 mL of 2% KI solution for each assay. After ozonation of the sample, it was filtered through a cellulose membrane filter with a pore size of 0.20 μm and later sent for analysis in HPLC. The FQ treatment together with the intermediate ozonation was named FQO, and the treated water sample was collected after the ozonation.

3. RESULTS AND DISCUSSION

3.1. Statistical analysis and model adjustment

RSM was developed taking into account all the considerable interactions in the CCD to optimize the crucial variables and explain the nature of the response surface in the experiment. Tables S1 and S2 (Supplementary material) present the results of the ANOVA for pre-ozonation and intermediate ozonation, respectively, for the two drugs studied. Furthermore, semi-experimental removal expressions for CAF and AMP in the pre-ozonation and intermediate ozonation stages predicted by the data analysis are available in Annex I of the supplementary material.

Considering the application of low (a) and high (b) flows, the LOF p values are, respectively, for the pre-ozonation tests as: CAF 0.020 (a) and 0.964 (b); AMP 0.016 (a) and 0.050 (b) and, for the intermediate ozonation tests: CAF 0.020 (a) and 0.337 (b); AMP 0.210 (a) and 0.739 (b). These values, despite not showing a significant adjustment in all cases, as in the application of high flow rates of ozone for the two drugs evaluated, generally confirm an adequate applicability of this method to evaluate the removal of CAF and AMP.

The validity of the polynomial model was evaluated by determining the coefficient of determination (R^2). For pre-ozonation, the values of $R^2_{caf} = 0.863$; $R^2_{amp} = 0.873$ and adjusted $R^2_{caf} = 0.701$; adjusted $R^2_{amp} = 0.730$ at low flow mean a relatively satisfactory relationship between the predicted and experimental data. As for the high flow, the values of $R^2_{caf} = 0.397$; $R^2_{amp} = 0.600$ and adjusted $R^2_{caf} = 0.0$; adjusted $R^2_{amp} = 0.151$ are considered statistically unsatisfactory. However, it is not possible to state and draw a meaningful conclusion from these data before evaluating other predictors. Thus, for the application of the model, it was taken into account how changes in the values of the predictor variables are associated with changes in the value of the response variable. For the intermediate ozonation, the values of $R^2_{caf} = 0.782$; $R^2_{amp} = 0.903$ and adjusted $R^2_{caf} = 0.600$; adjusted $R^2_{amp} = 0.882$ at low flow and, $R^2_{caf} = 0.846$; $R^2_{amp} = 0.915$ and adjusted $R^2_{caf} = 0.718$; adjusted $R^2_{amp} = 0.844$ at high flow, as in pre-ozonation, means a satisfactory relationship between predicted and experimental data.

A Pareto plot was used to illustrate the standardized influences of the independent variables and their effects on the dependent variable, at pre-ozonation (Figure 4(a)–4(d)) and at intermediate ozonation (Figure 4(e)–4(h)). The standardized effect of the related factor on the response is indicated by the length of each bar in the graph. Negative coefficients for the model indicate an undesirable or antagonistic effect on the removal efficiency of CAF and AMP, while positive coefficients show a desirable or synergistic effect on the removal efficiency of the compounds.

Still, in Figure 5(a)–5(h), one can observe the predicted values versus the observed values (R%) adjusted mainly by the straight line, for the POFQ and FQO tests. The linear relationship shows a standard error distribution and high applicability and accuracy of the model for favorable and real prediction of the results, ensuring that the method provides a sufficient approximation for the optimization process. Note that there is no clear pattern followed in the crude residues in relation to the observed response (Figure 6(a)–6(h)).

3.2. Effect of variables on the removal of CAF and AMP

3.2.1. Pre-ozonation

The interactive effects of independent parameters during CAF and AMP removal in pre-ozonation are demonstrated in 3D surface plots, respectively, in Figures 7 and 8.

Figure 7(a) shows the effect of variables when low flow ozone is applied for CAF removal. It can be seen in Figure 7(a.1) that an increase in the contact time and in the pH of the solution increases the percentage of CAF removal until ideal conditions are reached. Considering that the greater the amount of ozone in the system per unit of time, the greater the amount of molecules and/or hydroxyl radicals produced that react with the molecules of the studied compound (Vecchio 2019). Therefore, the gradual formation of these radicals during the process time period results in an increase in CAF deterioration from 66.9 to 92.4%. It is worth mentioning that the greatest production of hydroxyl radicals occurs in indirect reactions, where the pH of the solution is considered basic (Souza 2016; Camargo-Perea & Rubio-Clemente 2020; Montoya-Rodríguez et al. 2020). Figure 7(a.2) and 7(a.3) demonstrate the remarkable effect of coagulant concentration, time and pH on CAF removal
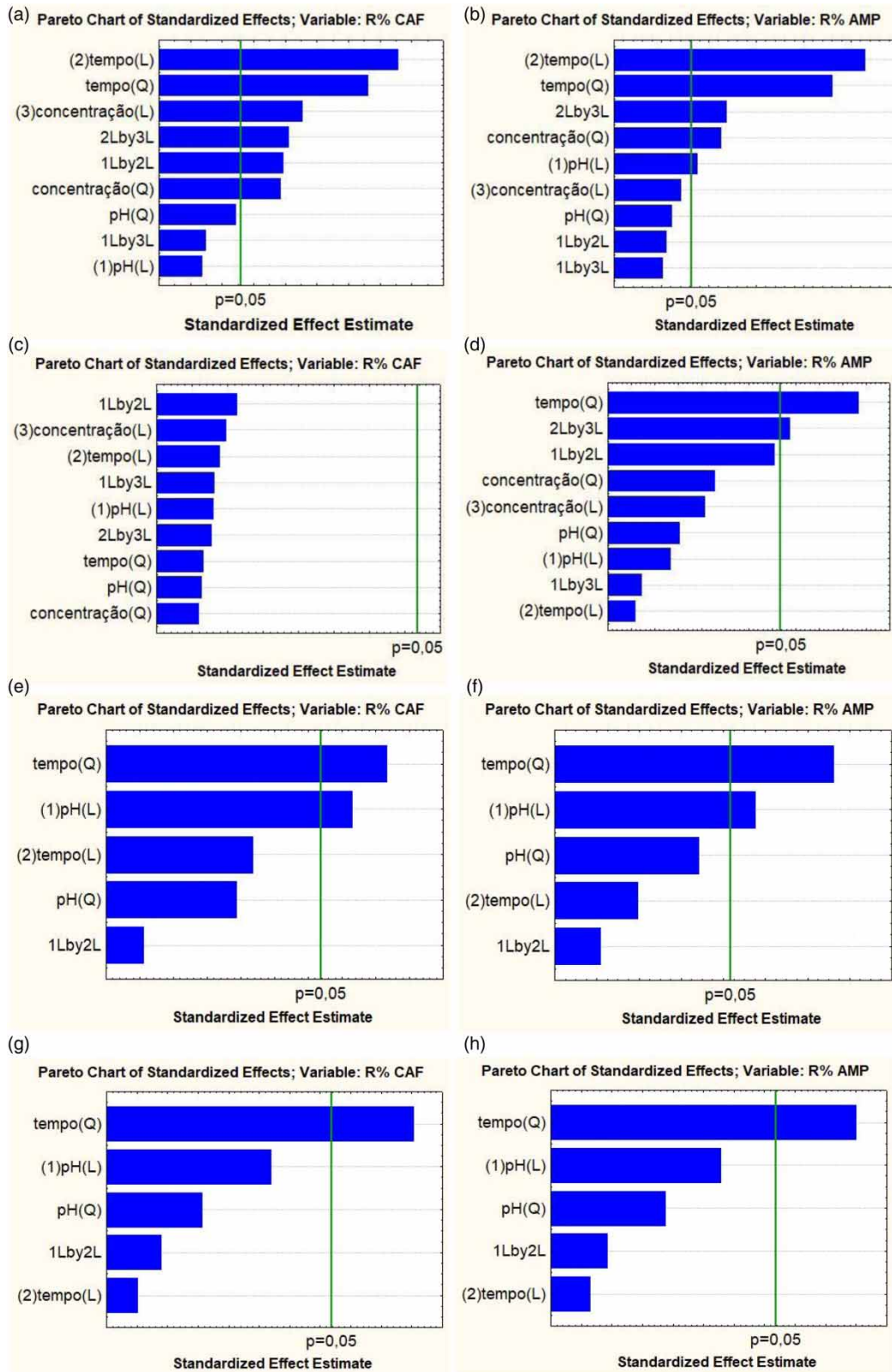
Figure 4 | Pareto chart of the main and interaction effects obtained from the central composite design for the POFQ tests: (a) CAF low flow, (b) AMP low flow, (c) CAF high flow and (d) CAF high flow and, in the FQO tests: (e) CAF low flow, (f) AMP low flow, (g) CAF high flow and (h) CAF high flow.
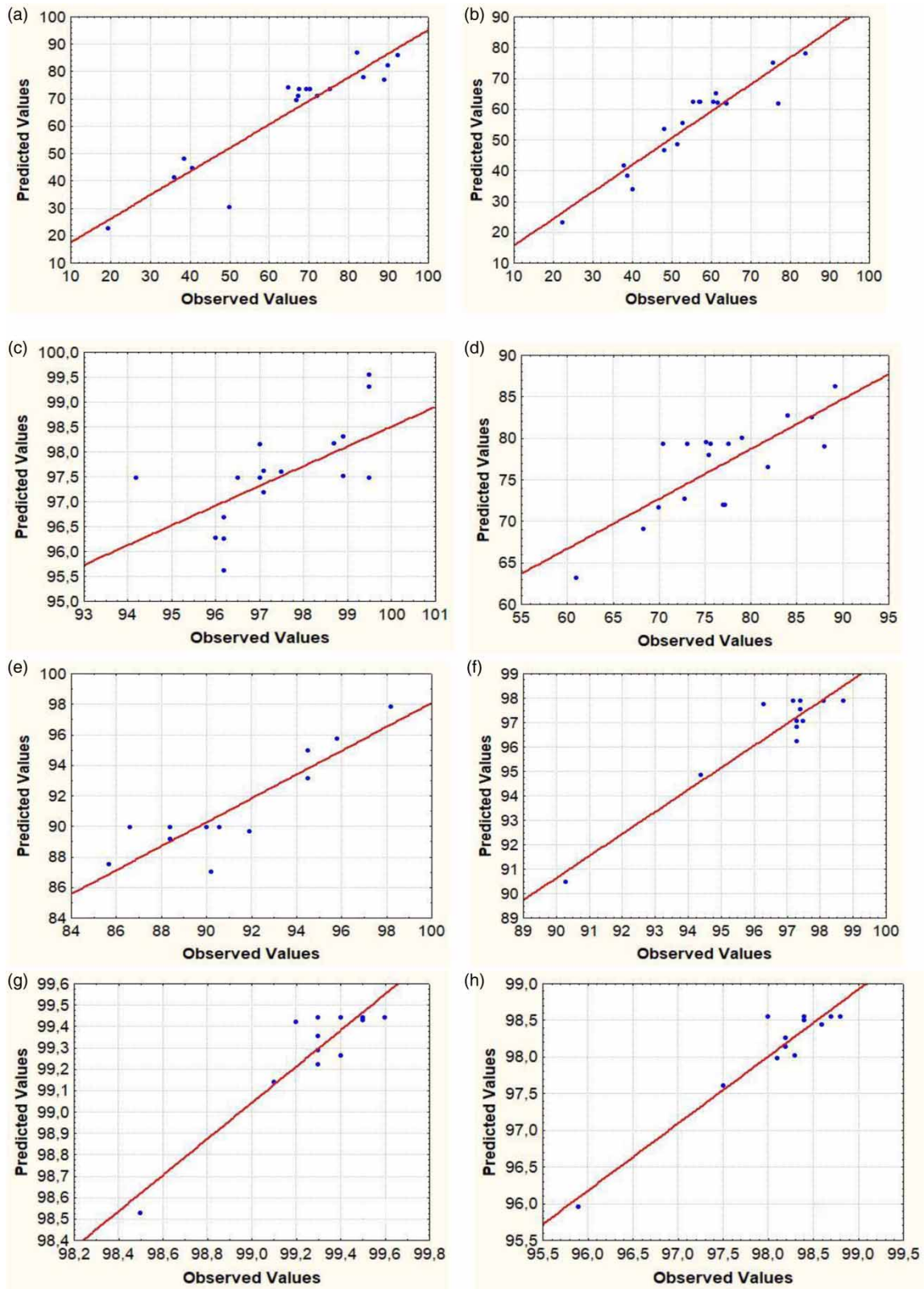
Figure 5 | Comparison of observed and predicted values for POFQ tests: (a) CAF low flow, (b) AMP low flow, (c) CAF high flow and (d) CAF high flow and, in the FQO tests: (e) CAF low flow, (f) AMP low flow, (g) CAF high flow and (h) CAF high flow.
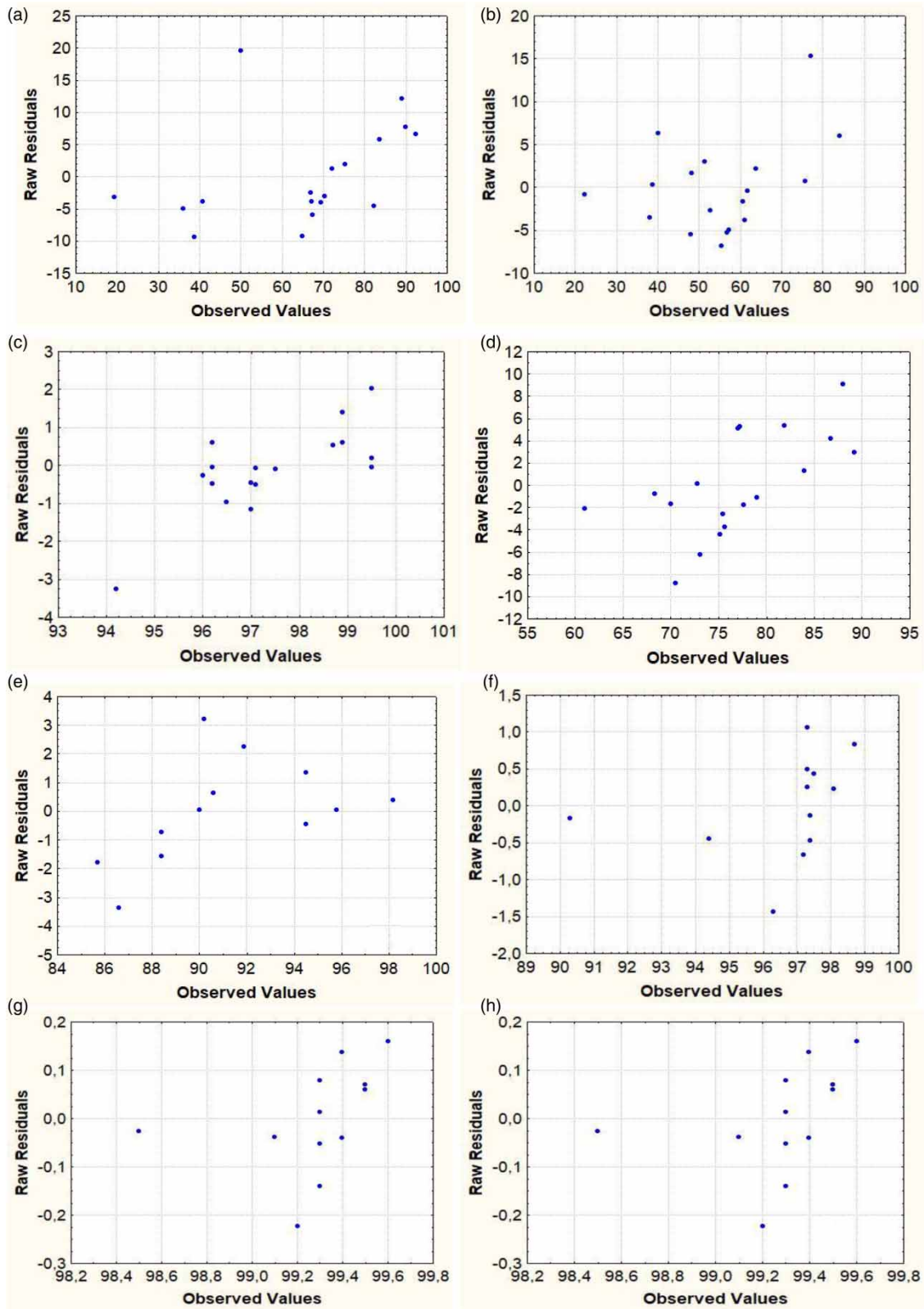
Figure 6 | Crude residues versus values observed for the POFQ tests: (a) CAF low flow, (b) AMP low flow, (c) CAF high flow and (d) CAF high flow and, in the FQO tests: (e) CAF low flow, (f) AMP low flow, (g) CAF high flow and (h) CAF high flow.
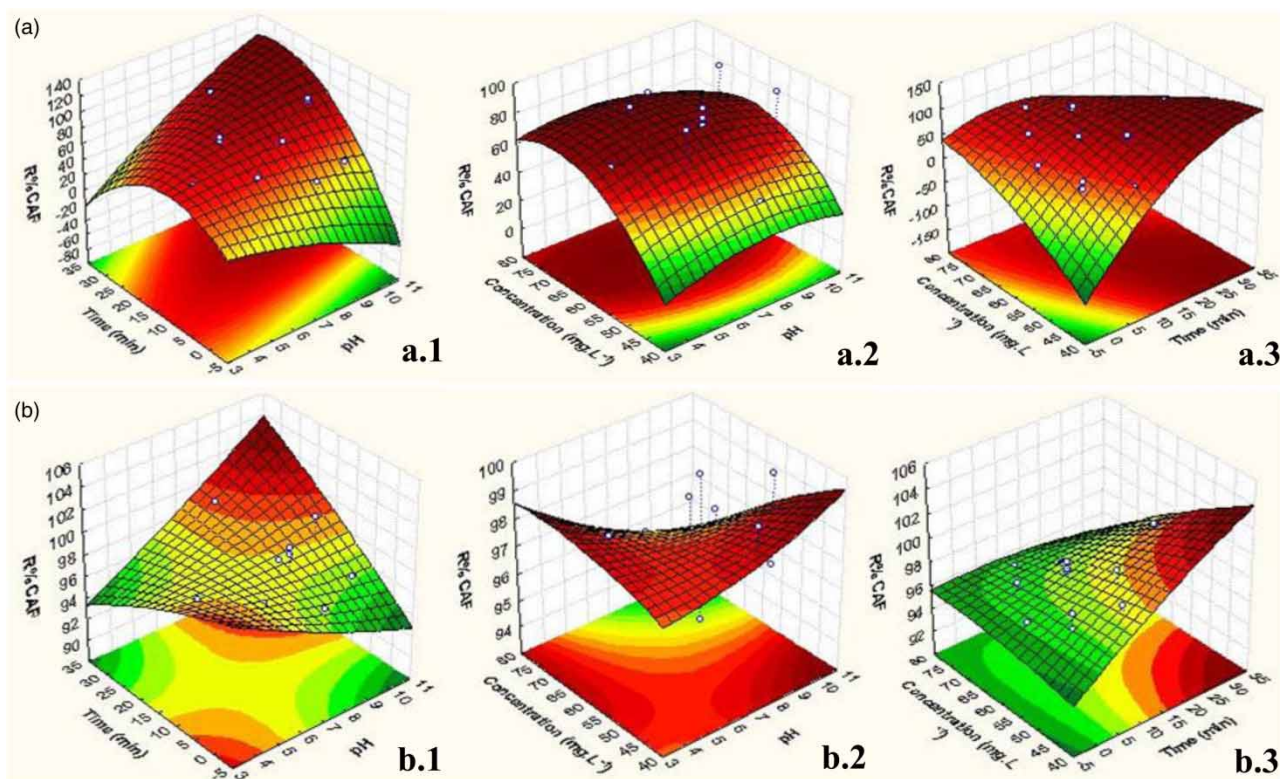
Figure 7 | Estimated response surface for the central composite design for CAF removal in POFQ tests: (a) low flow and (b) high flow.

performance. At first, it is apparent that the performance of pre-ozonation increases with increasing concentration of coagulant in relation to pH (a.2). However, in terms of contact time, the best CAF removals are obtained at the lowest coagulant concentrations. The same behavior can be observed in Figure 7(b.2) and (b.3), when a high flow rate of ozone is applied to remove the same drug.

Figure 8(a.2) and 8(b.2) demonstrate the effect of coagulant concentration in relation to solution pH on AMP removal. As with CAF removal, the best AMP removals took place at basic pH, where reactions with ozone are favored (Farjado *et al.* 2013). The same can be seen in Figure 8(b.1). It is also observed that the increase in the contact time with ozone in the system resulted in an increase in the removal of AMP in the aqueous solution, due to the strong interactions of the drug with the oxidizing gas (Figure 8(a.1) and (a.3)). Therefore, based on these figures and on the validation of data, it appears that the optimal removal of CAF and AMP for pre-ozonation, at low and high ozone flow rates, takes place at pH 10, contact time of 15 min and concentration of 52.5 mg·L^{-1} coagulant.

### 3.2.2. Intermediate ozonation

As with pre-ozonation, the interactive effects of independent parameters during CAF and AMP removal in intermediate ozonation are demonstrated in 3D surface plots, respectively, in Figures 9 and 10.

Figures 9 and 10, a and b, demonstrate the remarkable effect of pH in relation to ozonation time, for low and high flows, respectively, on the removal performance of both CAF and AMP. It is apparent that the removal performance increases with increasing pH in the intermediate ozonation method, improving the mass transfer process and increasing the dependence between drug and gas. Still, it is observed that the lower times are sufficient to obtain a good removal of the drugs, since, when compared to the low flow, there is a greater amount of ozone in the reaction even in shorter times. Based on these figures, the maximum drug removal is obtained in an ozonation time of 5 min. The results confirm that an increase in the pH of the solution causes an increase in the removal of pollutants. Optimal removal is achieved at pH 10.0. It is clear

Figure 8 | Estimated response surface for the central composite design for AMP removal in POFQ tests: (a) low flow and (b) high flow.
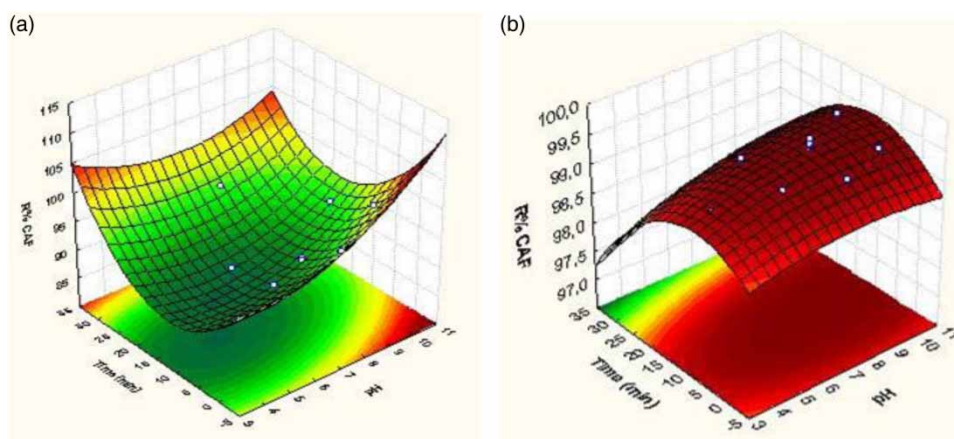
Figure 9 | Estimated response surface for the central composite design for CAF removal in FQO tests: (a) low flow and (b) high flow.
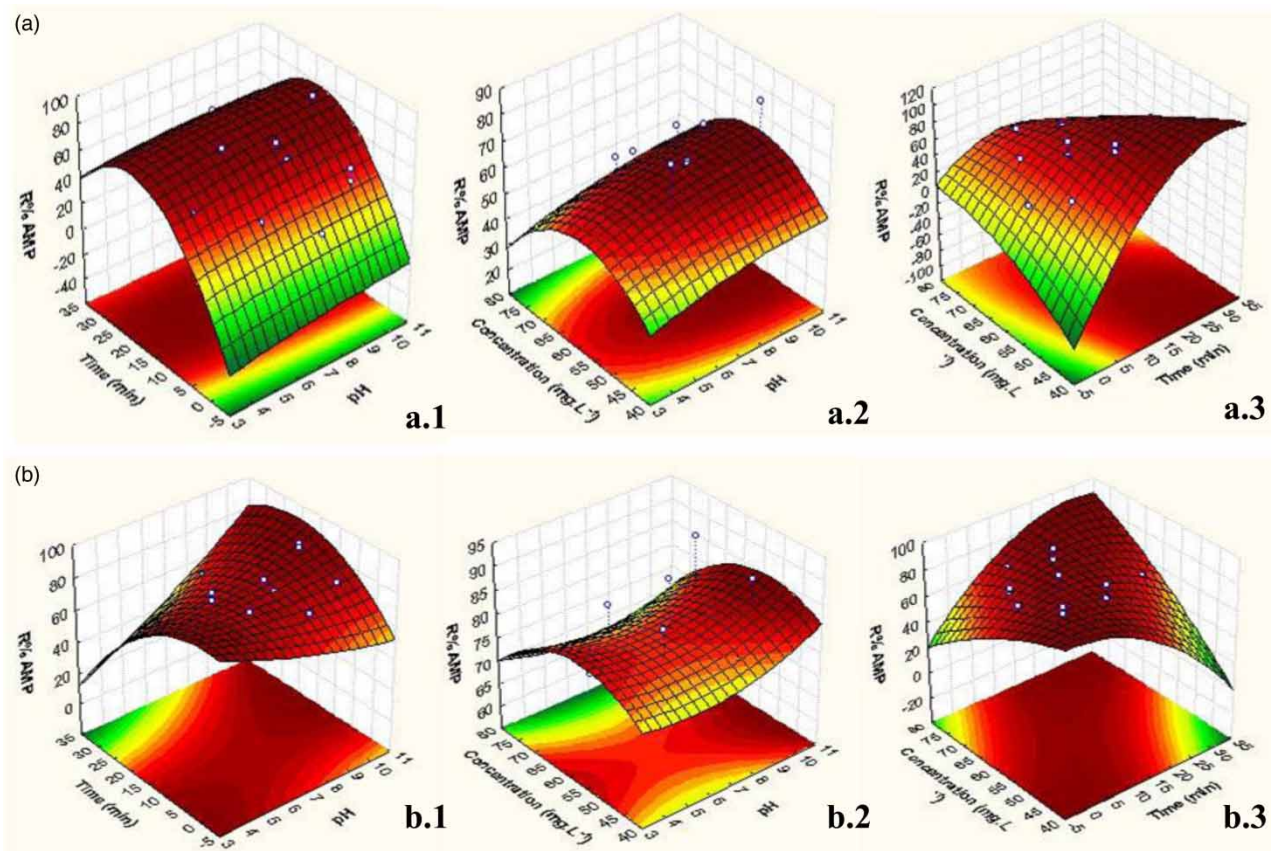
that at a higher solution pH, the formation of hydroxyl radicals is potentiated, amplifying the interaction of drugs with the radicals. In addition, reactions in a basic medium by themselves have a high oxidation potential and rapid reaction kinetics (Montoya-Rodríguez *et al.* 2020).
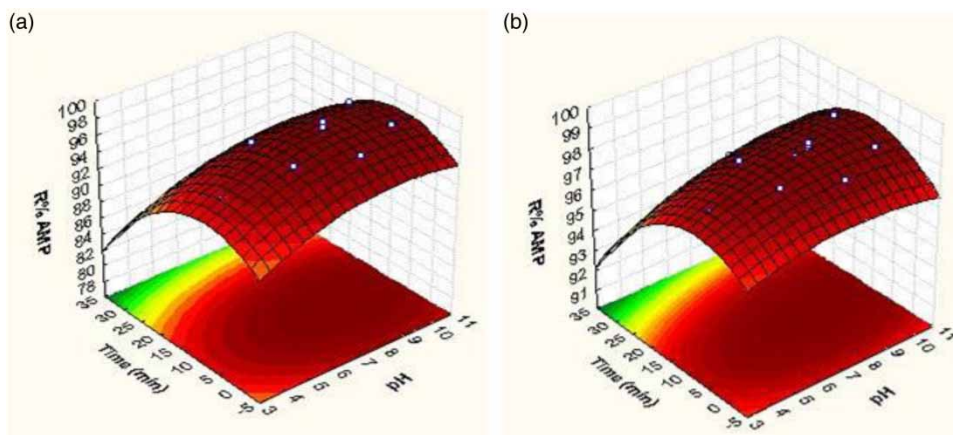
Figure 10 | Estimated response surface for the central composite design for AMP removal in FQO tests: (a) low flow and (b) high flow.

4. CONCLUSION

Based on the results obtained, it was confirmed that the synergy of the ozonation process with conventional water treatment is an effective, sensitive and fast method for the removal of CAF and AMP from the aqueous medium. Through the effects of experimental parameters on the percentage of drug removal studied by the experimental design methodology, it was observed that, in pre-ozonation, pH and ozonation time were the significant factors in the removal of both drugs. In the intermediate ozonation, pH was the only significant factor in AMP removal. Furthermore, the application of ozone in water treatment provides a reduction in the amount of substances used to regulate pH values and for coagulation. The relation of residual plots ensures that the method provides a sufficient approximation for the optimization process. It appears that the reactions in the basic medium (pH 10.0) in both proposals, presented a high oxidation potential and amplified the removal of drugs in the aqueous matrix. The 3D response surfaces showed, in general, the remarkable effect of all analyzed variables, with deterioration increments, both CAF and AMP, of approximately 30 and 20% in the two analyzed flows. Therefore, the suggested procedures showed good potential for the removal of CAF and AMP from Arroio Dilúvio, located in the city of Porto Alegre – RS, Brazil, confirming that the treatment of these compounds is a key factor for the remediation of a polluted river.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

CONFLICT OF INTEREST

The authors declare there is no conflict.

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