



## Removal of diclofenac by conventional drinking water treatment processes and granular activated carbon filtration



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### HIGHLIGHTS

- We evaluate the removal of diclofenac in conventional water treatment processes.
- Aquatic humic substances were used in the water of this study.
- The use of chlorine and chlorine dioxide as pre-oxidant were investigated.
- Conventional treatment followed by activated carbon filtration was also studied.
- Byproducts formed in the oxidation of diclofenac were identified by LC–MS/MS.

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### ABSTRACT

This study was carried out to evaluate the efficiency of conventional drinking water treatment processes with and without pre-oxidation with chlorine and chlorine dioxide and the use of granular activated carbon (GAC) filtration for the removal of diclofenac (DCF). Water treatment was performed using the Jar test with filters on a lab scale, employing nonchlorinated artesian well water prepared with aquatic humic substances to yield 20 HU true color, kaolin turbidity of 70 NTU and 1 mg L<sup>-1</sup> DCF. For the quantification of DCF in water samples, solid phase extraction and HPLC–DAD methods were developed and validated. There was no removal of DCF in coagulation with aluminum sulfate (3.47 mg Al L<sup>-1</sup> and pH = 6.5), flocculation, sedimentation and sand filtration. In the treatment with pre-oxidation and disinfection, DCF was partially removed, but the concentration of dissolved organic carbon (DOC) was unchanged and byproducts of DCF were observed. Chlorine dioxide was more effective than chlorine in oxidizing DCF. In conclusion, the identification of DCF and DOC in finished water indicated the incomplete elimination of DCF through conventional treatments. Nevertheless, conventional drinking water treatment followed by GAC filtration was effective in removing DCF (≥99.7%). In the oxidation with chlorine, three byproducts were tentatively identified, corresponding to a hydroxylation, aromatic substitution of one hydrogen by chlorine and a decarboxylation/hydroxylation. Oxidation with chlorine dioxide resulted in only one byproduct (hydroxylation).

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### 1. Introduction

The occurrence and fate of pharmaceutical compounds and their metabolites in the aquatic environment have been recognized as an emerging issue. There is concern because little is known regarding the potential effects of these compounds on non-target organisms, mainly chronic toxicity and possible additive effects of a vast range of pharmaceuticals present in the aquatic environment, even at trace levels (ng L<sup>-1</sup> or µg L<sup>-1</sup>) (Huang et al., 2011; Rodil et al., 2012).

The presence of pharmaceutical residues in effluents from wastewater treatment plants (WWTPs) shows that not all pharmaceuticals are completely removed during treatment (Zhang et al., 2008; Morasch et al., 2010; Rodil et al., 2012). Consequently, they have been widely found at concentrations in the ng L<sup>-1</sup>–µg L<sup>-1</sup> range in surface waters, which is the main source of raw water in drinking water treatment plants (DWTPs) (Vieno et al., 2007; Vulliet et al., 2011; Montagner and Jardim, 2011; Valcárcel et al., 2011a,b) and groundwater (Lapworth et al., 2012). Due to their inefficient treatment in DWTPs and their hydrophilic properties, a number of pharmaceuticals have also been found in drinking water at concentrations in the order of ng L<sup>-1</sup> (Ziyilan and Ince, 2011; Vulliet et al., 2011; Valcárcel et al., 2011a,b; Rodil et al., 2012).

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Among the most consumed non-steroidal anti-inflammatory drugs frequently found in aquatic environments are aspirin, acetaminophen, ibuprofen, naproxen and diclofenac (DCF) (Fent et al., 2006). The DCF has been found in drinking water at concentrations  $<10 \text{ ng L}^{-1}$  (Rabiet et al., 2006; Vulliet et al., 2011).

Although the pharmaceuticals are still not regulated in drinking water, it is of great importance to know if the treatments applied to DWTPs can eliminate pharmaceutical compounds. Moreover, little is known about the occurrence and fate of byproducts (metabolites and transformation products) formed during drinking water treatments and their (eco)toxicological effects (Touraud et al., 2011). Research on the possible byproducts formed through the biodegradation and chlorination of some pharmaceuticals during treatments at WWTPs and DWTPs has been reported (Quintana et al., 2005, 2010; Soufan et al., 2012). However, no study has reported on the byproducts of DCF formed by oxidation with chlorine dioxide.

Conventional treatments have been reported ineffective in the removal of most pharmaceuticals, with an efficiency of  $<5\text{--}40\%$  (Vieno et al., 2007; Pojana et al., 2011). However, processes and unit operations, such as ozonation (Ikehata et al., 2006), adsorption on activated carbon (Kim et al., 2007) and membrane filtration, such as nanofiltration and reverse osmosis (Radjenovic et al., 2008; Boleda et al., 2011), have shown effective in the removal of a relatively large number of pharmaceuticals ( $>99\%$ ). In general, the percentage removed depends on several factors, such as molecular structure of pharmaceuticals, type and dosage of coagulant, presence and characteristics of dissolved organic matter (DOM), mechanism of coagulation and experimental conditions (Vieno et al., 2007; Pojana et al., 2011). Nevertheless, the use of advanced processes in DWTPs is still limited due to their high cost, especially in developing countries, as Brazil.

Most studies on the removal of pharmaceuticals have focused on a small set of processes or operations of water treatment. Moreover, they have used humic substances extracted from peat instead of water, which have different characteristics, including a lower content of humic acids than fulvic acids, molecules of lower molecular weight and less condensed structures, which may hinder the removal of pharmaceuticals (Rigobello et al., 2011).

This study was carried out to evaluate the efficiency of conventional drinking water treatment processes (coagulation, flocculation, sedimentation, sand filtration and chlorine disinfection) combined with pre-oxidation using chlorine and chlorine dioxide and adsorption on granular activated carbon (GAC) in the removal of DCF in water containing aquatic humic substances (AHSs). Additionally, the byproducts formed during the oxidation of DCF with chlorine and chlorine dioxide were tentatively identified by LC-MS/MS. The selection of the analyte DCF was based on its high consumption, high frequency of detection in the aquatic environment and low biodegradability and polarity, which favor its spread in natural waters (Vieno et al., 2007; Zhang et al., 2008).

## 2. Materials and methods

### 2.1. Chemicals and reagents

Acetonitrile and methanol were of HPLC grade (Baker) and high-purity water was obtained from a Milli-Q water system (Millipore) equipped with a UV radiation source. The coagulant used was a commercial liquid of aluminum sulfate ( $\text{Al}_2(\text{SO}_4)_3 \cdot 14.3\text{H}_2\text{O}$ , 50%, w/w) containing 7.3%  $\text{Al}_2\text{O}_3$  (w/w) with specific density of  $1.3 \text{ g cm}^{-3}$  and 3.85% aluminum (w/w). The chlorine dioxide solution ( $300 \text{ mg ClO}_2 \cdot \text{L}^{-1}$ ) generated from the sodium chlorate was supplied by Eka Chemicals SA of Brazil – Akzo Nobel Company. The chlorine solution was prepared from a solution of sodium hypochlorite with 12.9% active

chlorine and  $1.22 \text{ g cm}^{-3}$  density provided by the DWTP of São Carlos – SP, Brazil. The solutions of chlorine and chlorine dioxide were prepared at the desired concentrations by dilution with water (Milli-Q system,  $18.2 \text{ M}\Omega \text{ cm}$  at  $25^\circ\text{C}$ ). The analytical standard of DCF (sodium salt, CAS number 15307-79-6) had  $>99\%$  purity and was supplied by Sigma–Aldrich. DCF has a  $K_{\text{ow}}$  of 4.51 and a  $\text{pK}_a$  of 4.15 (Vieno et al., 2007). A stock solution of DCF was prepared in methanol at a concentration of  $200 \text{ mg L}^{-1}$  and stored in a refrigerator at  $4^\circ\text{C}$ .

### 2.2. Water sample collection and extraction of AHS

The AHS used to adjust the color of the synthetic water samples were extracted from the water collected in a tributary of the Itapanhaú River (Latitude  $23^\circ47'19.35'' \text{ S}$  and Longitude  $46^\circ3'29.32'' \text{ W}$ ) in Bertioga, São Paulo, Brazil (tropical forest). The AHS were isolated by adsorption chromatography on XAD-8 non-ionic macroporous resin (Supelco) according to the method of Thurman and Malcolm (1981). The water samples collected exhibited a true color of 184 HU, turbidity of 4.38 NTU,  $\text{pH} = 4.9$ , dissolved organic carbon (DOC) of  $17.4 \text{ mg C L}^{-1}$ , alkalinity of  $6 \text{ mg CaCO}_3 \text{ L}^{-1}$  and UV absorbance at a wavelength of 254 nm ( $\text{UV}_{254}$ ) of 4.79. Overall, characterization results indicated that the AHS fraction contained a greater aliphatic than aromatic carbon content and a relatively high percentage of oxygen atoms (higher content of fulvic acids than humic acids). The AHS were characterized as described by Rigobello et al. (2011).

### 2.3. Analytical methods

The turbidity of the samples was measured using a HACH 2100P turbidity meter. A Shimadzu 5000A total organic carbon (TOC) analyzer spectrophotometer was used to determine the DOC content in the water samples.  $\text{UV}_{254}$  and color were measured by a HACH DR4000 spectrophotometer at 254 and 455 nm, respectively. All samples were filtered through a  $0.45 \mu\text{m}$  membrane (Millipore, cellulose ester, 90 mm diameter) prior to both  $\text{UV}_{254}$  and  $\text{UV}_{278}$ , DCF and DOC analyses to remove particles. The pH of the water samples was measured using an Orion 420A potentiometer. The chlorite ion present in the water samples after the pre-oxidation with chlorine dioxide was determined by a colorimetric method with a Prominent DT4 instrument. The UV/Vis analysis was performed using a UV/Vis JASCO – 630 V spectrophotometer. The concentrations of  $\text{Cl}_2$  and  $\text{ClO}_2$  were quantified by reaction with N,N-diethyl-p-phenylene diamine (DPD) using a HACH DR4000 spectrophotometer at 530 nm. The analysis of  $\text{ClO}_2$  with DPD was performed according to the manufacturer's instructions.

#### 2.3.1. HPLC-DAD analysis

The DCF was extracted from the water samples using solid phase extraction (SPE) with Phenomex  $\text{C}_{18}$  sorbent (6 mL; 500 mg of resin weight). Each  $\text{C}_{18}$  sorbent was pre-conditioned with 5 mL of methanol and 5 mL of purified water (Milli-Q) at a flow rate of  $2 \text{ mL min}^{-1}$ . Next, 100 mL of water ( $\text{pH}$  between 6.0 and 8.0) was passed through the  $\text{C}_{18}$  sorbent at a flow rate of  $5 \text{ mL min}^{-1}$ . The DCF was eluted with 5 mL of methanol in a volumetric flask. The samples were then analyzed on an HPLC coupled to a DAD detector operating at  $\lambda = 278 \pm 4 \text{ nm}$  (Agilent Technologies) with an autosampler using a Zorbax  $\text{C}_{18}$  ( $250 \text{ mm} \times 4.6 \text{ mm}$  id  $\times 5 \mu\text{m}$  particles) column. The flow rate was  $0.8 \text{ mL min}^{-1}$ , the injection volume was  $20 \mu\text{L}$ , the column oven was set to  $25^\circ\text{C}$  and the retention time was 10 min. An isocratic mobile phase of acetonitrile:water (65:35, v/v) was used and both components were acidified with 0.05% trifluoroacetic acid (99.9% purity).

The method employed was validated according to resolution number 899 of the National Agency of Sanitary Vigilance (ANVISA, 2003). The limit of quantification (LOQ) was  $3 \mu\text{g L}^{-1}$  and the limit

of detection (LOD) was  $2 \mu\text{g L}^{-1}$ . The method was successfully applied to determine DCF concentrations in the water samples ranging from 3 to  $1200 \mu\text{g L}^{-1}$ . The correlation coefficients ( $r$ ) were  $>0.99$ , the relative standard deviations  $<15\%$  and the accuracy between 96% and 108% for both curves. The mean intra- and inter-day reproducibility ranged from 96% to 101%, the relative standard deviations were below 15%, the recovery of the DCF concentrations ranged from 94% to 101% and the accuracy from 97% to 107% through three spiking levels in synthetic water: 3, 500 and  $1000 \mu\text{g DCF L}^{-1}$ . Samples with known concentrations of DCF were prepared in purified water (Milli-Q) and in synthetic water (containing AHS and kaolin) to examine the specificity of the method. The organic matrix did not interfere with the analyte detection.

### 2.3.2. LC-MS/MS (ion trap)

For the separation and identification of the byproducts of DCF formed in the oxidation with chlorine and chlorine dioxide, SPE was employed as described previously. This extraction was followed by LC using HPLC SHIMADZU LC-20A and an autoinjector with a UV detector coupled to a spectrometer mass (MS) and an ion trap analyzer (Bruker). The chromatographic separation was performed as described for the HPLC-DAD analysis, but the mobile phase was not acidified and the injected sample volume was  $50 \mu\text{L}$ .

The ionization of the compounds was achieved by electrospray in negative mode and quasi-molecular ions were detected from the loss of a proton, characterized as  $[\text{M}-\text{H}]^-$ . An initial analysis in MS mode was performed over a full scan to detect compounds and fragmentation experiments were performed to confirm the compounds detected.

### 2.4. Preparation of synthetic water

Nonchlorinated water extracted from an artesian well (turbidity =  $<0.2$  NTU; apparent color =  $<2$  HU; pH = 6.2; aluminum =  $<0.01 \text{ mg Al L}^{-1}$ ; DCF = not detected) was used to prepare synthetic water with AHS to yield  $20 \pm 1$  HU true color and kaolin to yield turbidity of  $70 \pm 2$  NTU (typical characteristics during the rainy season in the region of São Carlos, São Paulo, Brazil) and spiked with  $1 \text{ mg L}^{-1}$  DCF (sodium salt, Sigma–Aldrich, purity  $>99\%$ ). The concentration of DCF was based on the LOQ of the method. The water samples were stored for up to 1 week at room temperature. The resulting alkalinity was between 22 and  $23 \text{ mg CaCO}_3 \text{ L}^{-1}$ . The absorbance measurements and DOC were performed using water samples filtered through a  $0.45 \mu\text{m}$  membrane of cellulose acetate. Absorbance and pH measurements were performed without adding sodium thiosulfate to the samples.

### 2.5. Water treatment tests

Conventional water treatment tests were carried out using the Jar test (ETICA) with six square beakers (2 L), which provided velocity gradients in the  $10\text{--}1200 \text{ s}^{-1}$  range and two kits of six bench-scale filter columns with internal diameters of 19 mm in series. Six filters were filled with a 15 cm layer of sand, and the other six filters were filled with a 15 cm layer of GAC, both with grain sizes ranging from 0.30 to 0.59 mm. The following parameters were adopted for the tests: rapid mixing (time = 10 s; velocity gradient rapid mixing =  $1000 \text{ s}^{-1}$ ), flocculation (time = 20 min; velocity gradient flocculation =  $15 \text{ s}^{-1}$ ), sedimentation (velocity =  $1 \text{ cm min}^{-1}$ ), filtration rate (sand/GAC filters =  $60 \text{ m}^3 \text{ m}^{-2} \text{ d}^{-1}$ ), filtration time after sedimentation (sand/GAC filters = 20 min) and empty bed contact time (sand/GAC filters = approximately 3.6 min). The temperature of the water during the Jar test trials was kept at approximately  $20 \text{ }^\circ\text{C}$ . The sand filters were conditioned with deionized water prior to passing settled decanted water through them and were cleaned

after each different experimental test trial with tap water in ascendant flow for 10 min.

Extensive Jar testing for coagulation, flocculation and sedimentation (22 Jar tests with six jars) were conducted to define the zones of optimum turbidity removal in settled water to  $\leq 5$  NTU, for water samples without DCF. A solution of NaOH was used prior to the addition of aluminum sulfate to vary the coagulation pH.

After finding the optimum zone for the removal of turbidity ( $\leq 5$  NTU) in settled water by coagulation, flocculation and sedimentation, three aluminum doses ( $3.5$ ,  $4.2$  and  $5.0 \text{ mg Al L}^{-1}$ ) and coagulation pH values ( $6.5$ ,  $6.7$  and  $6.6$ , respectively) were chosen based on the lowest turbidity values ( $1.8 \pm 0.1$  NTU) and color ( $10 \pm 1$  HU). This selection was performed to evaluate the removal of DOC, DCF and minimize residual aluminum by coagulation, flocculation, sedimentation and sand filtration.

Because there was no difference in the removal of DOC and DCF for the three doses of coagulant, an aluminum dose and coagulation pH ( $3.46 \text{ mg Al L}^{-1}$  and pH 6.5) were selected based on the lowest concentration of residual aluminum ( $\leq 0.1 \text{ mg L}^{-1}$ ), color, turbidity of the filtrated water and lowest doses of NaOH and coagulant required.

Following sand and GAC filtration, the water was disinfected by adding sodium hypochlorite at  $5 \text{ mg Cl}_2 \text{ L}^{-1}$ . The contact time for disinfection was 30 min and 24 h. In the experiments, 250 mL of water were used in a capped amber vial under constant agitation (100 rpm) at  $20 \text{ }^\circ\text{C}$ . This test was performed in duplicate for each contact time. The chlorine reaction was stopped by the addition of sodium thiosulfate.

The doses of chlorine and chlorine dioxide used in the pre-oxidation were selected based on the residual oxidant concentration (approximately  $0.1 \text{ mg L}^{-1}$ ) to avoid interference with the adsorption of DCF on GAC. Typically, 50–70% of the chlorine dioxide applied becomes chlorite ions, which limits the dosage of this oxidant in DWTPs to, at most,  $1.4 \text{ mg L}^{-1}$  and the total combined dioxide chlorine, chlorite and chlorate to  $1 \text{ mg L}^{-1}$  (USEPA, 1999). In Brazil, Ordinance n. 518/2004 of the Health Ministry (URL, Ministry of Health, 2004) was repealed and has recently reemerged as Ordinance 2914 of December 2011, changing the maximum amount of chlorite in treated water from 0.2 to  $1.0 \text{ mg L}^{-1}$  (URL, Ministry of Health, 2011). Therefore, the chlorine dioxide dose chosen for the pre-oxidation was smaller than or equal to  $0.2 \text{ mg chlorite L}^{-1}$  because Ordinance 518/2004 (URL, Ministry of Health, 2004) was in force during this study. The doses of the oxidants selected and contact times for the pre-oxidation followed by conventional treatment and adsorption on GAC were:  $0.25 \text{ mg ClO}_2 \text{ L}^{-1}$  with contact time of 30 min and  $1 \text{ mg Cl}_2 \text{ L}^{-1}$  with contact time of 1 h. The coagulation pH was adjusted using a NaOH solution.

The GAC used was produced from the babaçu coconut shell (Tobasa, Brazil) with  $957 \text{ mg g}^{-1} \text{ I}_2$ , density of  $0.452 \text{ g cm}^{-3}$ , 7.0% humidity and particle size between 0.30 and 0.59 mm. The isotherm was evaluated on a logarithmic scale according to the Freundlich isotherm (ASTM Standards: D 3860-98). The value of  $K_F$  was equal to 79 and  $1/n$  was equal to 0.16. The linear coefficient was 0.94. GAC filtration was performed after the sand filtration.

### 2.6. DCF oxidation experiments for the identification of byproducts

DCF oxidation experiments were performed with 250 mL of purified water (Milli-Q) at pH 6.0 and spiked with  $1 \text{ mg L}^{-1}$  DCF for the identification of byproducts. The doses of chlorine and chlorine dioxide were  $5 \text{ mg Cl}_2 \text{ L}^{-1}$  and  $1.4 \text{ mg ClO}_2 \text{ L}^{-1}$ , respectively. Parallel control samples (without DCF) were also studied. After 24 h, the reactions were quenched with ascorbic acid ( $0.5 \text{ mg mL}^{-1}$ ) and two 100 mL aliquots of this solution were extracted by SPE and analyzed by LC-UV and MS, as previously described.

**Table 1** Removal of DCF in conventional treatment (CT) processes combined with pre-oxidation with chlorine (POCl<sub>2</sub>) and chlorine dioxide (POClO<sub>2</sub>) and granular activated carbon (GAC) filtration.

Sample (n = 6)	Drinking water treatment processes														
	CT + GAC			POCl <sub>2</sub> + CT + GAC			POClO <sub>2</sub> + CT + GAC								
	DOC range (mg L <sup>-1</sup> )	DCF range (μg L <sup>-1</sup> )	%R	Abs <sub>254</sub> /Abs <sub>278</sub> <sup>a</sup>	pH	DOC range (mg L <sup>-1</sup> )	DCF range (μg L <sup>-1</sup> )	%R	Abs <sub>254</sub> /Abs <sub>278</sub> <sup>a</sup>	pH	DOC range (mg L <sup>-1</sup> )	DCF range (μg L <sup>-1</sup> )	%R	Abs <sub>254</sub> /Abs <sub>278</sub> <sup>a</sup>	pH
Synthetic water without DCF	5.7–5.9	ND	-	0.018/0.008	6.8	5.9–6.0	ND	-	0.019/0.008	6.9	5.9–6.0	ND	-	0.019/0.008	6.9
Synthetic water with DCF	20.1–22.9	1022–1026	-	0.035/0.045	6.7	23.4–25.1	1011–1016	-	0.035/0.042	6.9	23.4–25.1	1011–1016	-	0.035/0.042	6.9
Settled water	19.2–21.0	1004–1020	<0.5	0.031/0.045	7	-	-	-	-	-	-	-	-	-	-
SANDF	19.0–20.6	1025–1041	0	0.024/0.042	7.1	22.5–23.0	859–860	15 ± 1.5	0.030/0.037	7.3	20.8–22.9	758–759	25 ± 2.0	0.033/0.046	7.1
GACF	1.1–1.5	ND	≥99.7	0.000/0	9.3	1.2–1.4	ND	≥99.7	0.000/0.000	9.3	1.2–1.4	ND	≥99.7	0.000/0.000	9.2
Disinfection 30 min after SANDF	19.8–20.7	667–668	35 ± 0.1	-	7.4	-	-	-	-	-	-	-	-	-	-
Disinfection 24 h after SANDF	19.4–20.6	31–30	97 ± 1.8	-	7.6	-	-	-	-	-	-	-	-	-	-
Disinfection 30 min after GACF	0.9–1.1	ND	≥99.7	-	9.5	1.1–1.2	ND	≥99.7	0.004/0.002	9	1.0–1.2	ND	≥99.7	0.000/0.000	9.2
Disinfection 24 h after GACF	0.8–0.94	ND	≥99.7	-	9.6	1.0–1.1	ND	≥99.7	0.004/0.002	9.1	1.1–1.2	ND	≥99.7	0.000/0.000	9.2

n: number of samples; %R: percent removal of diclofenac ± relative standard deviation. ND: not detected up to 2 μg DCF L<sup>-1</sup>; CT: conventional treatment; POCl<sub>2</sub>: pre-oxidation with chlorine; POClO<sub>2</sub>: pre-oxidation with chlorine dioxide; SANDF: sand-filtered water; GACF: GAC-filtered water.  
<sup>a</sup> Water samples filtered through 0.45 μm membrane.

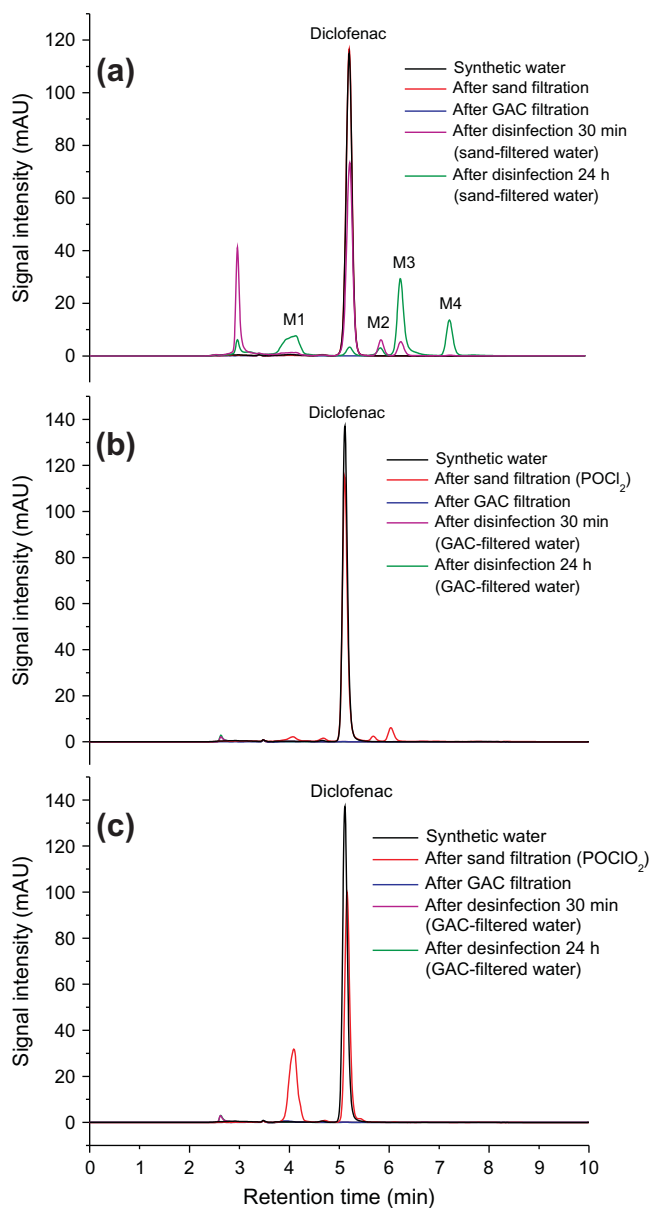
**3. Results and discussion**

**3.1. DCF removal through treatment processes**

The results of the parameters analyzed in the synthetic water with DCF and after conventional treatment with and without pre-oxidation with chlorine and chlorine dioxide and GAC filtration are shown in Table 1 and Figs. 1–3 for the optimized aluminum dose and coagulation pH (3.5 mg Al L<sup>-1</sup> and pH 6.5).

Table 1 shows that the synthetic water without DCF (blank) had low content of DOC, absorbance at 254 and 278 nm and no DCF detected by HPLC-DAD.

The results of the bench-scale tests with synthetic water without DCF (DOC range 5.7–5.9 mg L<sup>-1</sup>) showed that the removal of DOC was very low in the sand filtration (approximately 1.5 mg L<sup>-1</sup>), whereas the removal of color (<1 HU) and turbidity



**Fig. 1.** HPLC-DAD chromatograms of water samples after conventional drinking water treatment processes: (a) without pre-oxidation followed by GAC filtration; (b) with pre-oxidation with chlorine (POCl<sub>2</sub>) followed by GAC filtration and disinfection and (c) with pre-oxidation with chlorine dioxide (POClO<sub>2</sub>) followed by GAC filtration and disinfection.

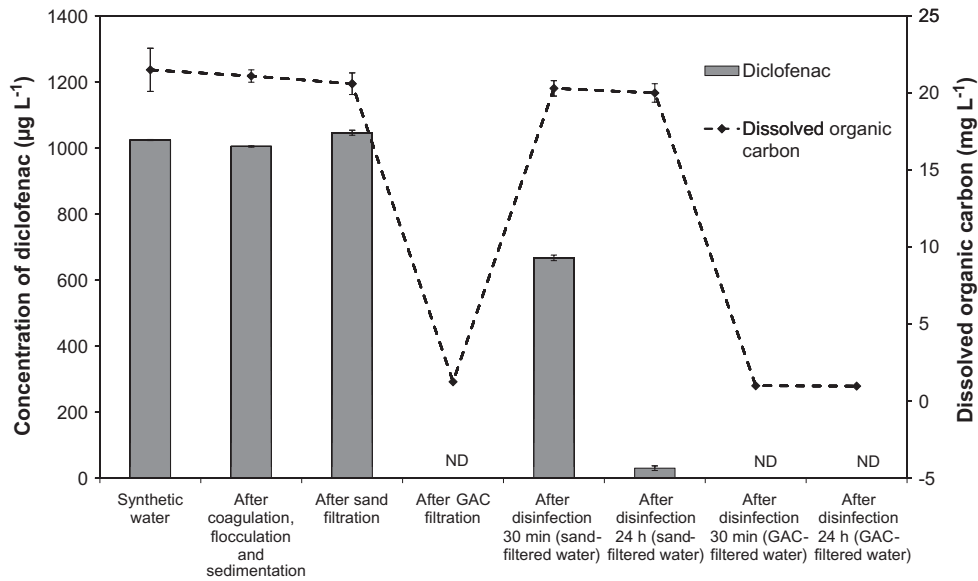


Fig. 2. Removal of DCF and DOC by conventional drinking water treatment processes without pre-oxidation and GAC filtration.

(<0.50 NTU) were high. However, the removal of DOC was high on GAC filtration (approximately 4.5 mg L<sup>-1</sup>).

### 3.1.1. Conventional treatment without pre-oxidation followed by GAC filtration

Table 1 shows that even under optimized conditions of color removal ( $10 \pm 1$  HU) and turbidity ( $1.8 \pm 0.1$  NTU), the conventional treatment (coagulation with 3.5 mg Al L<sup>-1</sup> and pH 6.5, flocculation, sedimentation and sand filtration) was not effective in removing DCF because no significant difference was found between the concentration of DCF in the synthetic water (1024 µg L<sup>-1</sup>) and that after sand filtration (1033 µg L<sup>-1</sup>). This difference was approximately 1% and the accuracy values were 102% (synthetic water) and 103% (sand-filtered water), which are in the 85–115% range accepted by most regulatory bodies for the chromatographic analysis of pharmaceuticals (ICH, 1995; ANVISA, 2003). However, the conventional treatment was effective in removing color and turbidity (sand-filtered water with apparent color  $\leq 1$  HU and turbid-

ity  $\leq 0.50$  NTU). These results are in agreement with those reported in the literature, which refer to a reduction in the concentration of DCF to less than 5% by coagulation with aluminum sulfate, flocculation, sedimentation and sand filtration (Vieno et al., 2010). In general, these processes are not efficient in removing the majority of pharmaceuticals from water (Kim et al., 2007; Pojana et al., 2011). In Ternes et al. (2002), the ineffectiveness of sand filtration was linked to the poor adsorption of the hydrophilic drug on the surface of sand.

According to the literature data, the removal of pharmaceuticals by coagulation is influenced mainly by the type and dose of coagulant, the presence and characteristics of the DOM, particularly humic substances, the coagulation pH, the coagulation mechanism and the molecular structure of the compounds to be removed (Vieno et al., 2010).

After the disinfection of the sand-filtered water for 30 min and 24 h of contact time, approximately 50% of the initial dose of chlorine were consumed and the concentration of DCF was reduced

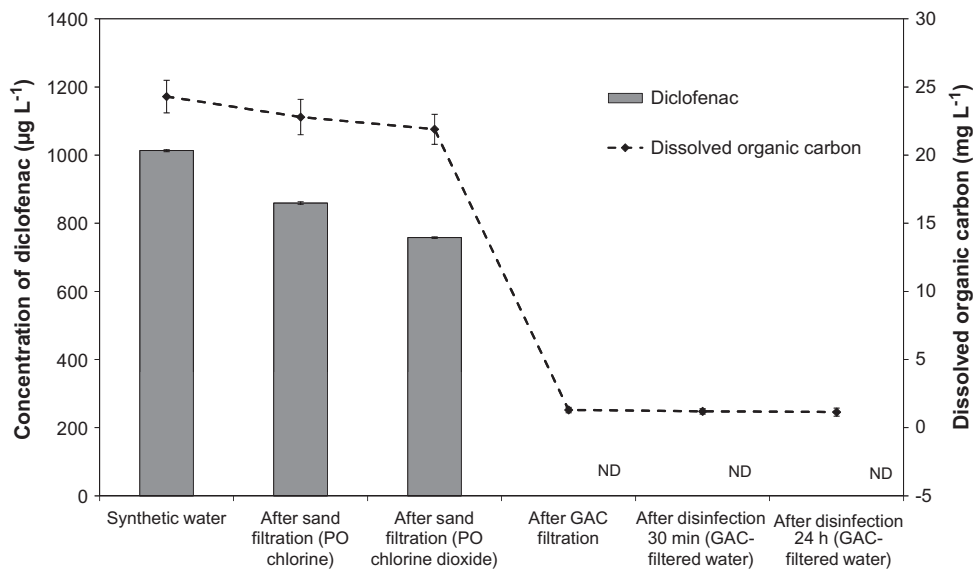


Fig. 3. Removal of DCF in different stages of conventional drinking water treatment with pre-oxidation (PO) using chlorine and chlorine dioxide followed by GAC filtration.

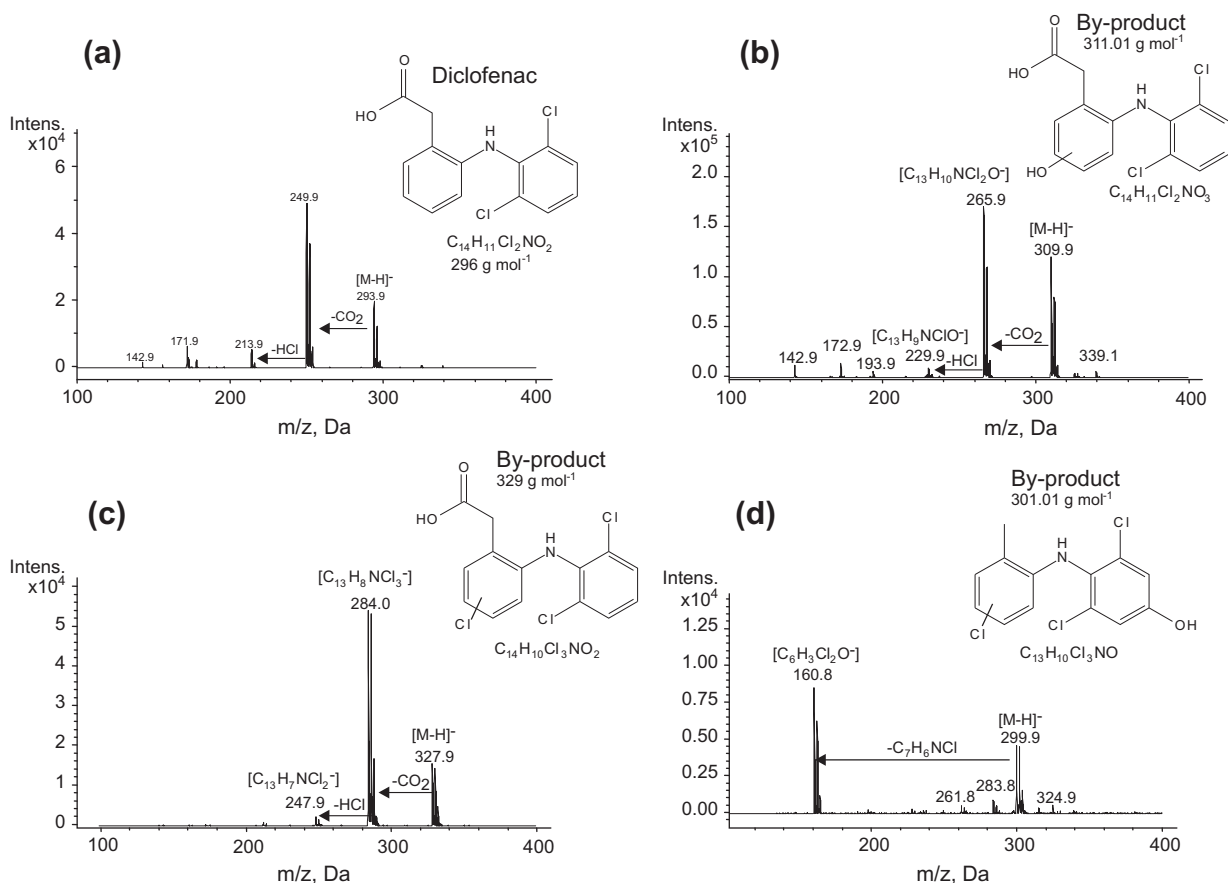


Fig. 4. Mass spectra (LC-MS) and proposed chemical structure of DCF and byproducts after oxidation with chlorine and chlorine dioxide.

more significantly after 24 h (approximately 97% reduction) (Table 1). Chlorine proved to be an effective oxidant for removing DCF (under the conditions studied), but because the concentration of DOC remained virtually the same as in the synthetic water (Fig. 2), the DCF was not mineralized and byproducts were formed.

The oxidation of DCF by chlorine generated several byproducts (M1, M2, M3 and M4), as indicated by HPLC-DAD (Fig. 1a). Several of these byproducts were tentatively identified by LC/MS/MS in samples after oxidation with chlorine (24 h) in purified water (Milli-Q), which led to the proposed structures shown in Fig. 4.

In the LC-MS chromatogram of oxidized purified water, a peak before DCF at 4.1 min was identified and its MS spectrum revealed a molecular ion at  $m/z$  310 Da and two additional ion fragments at  $m/z$  266 and 230 (Fig. 4b). This molecular ion corresponded to the addition of oxygen and loss of hydrogen. The MS/MS fragmentation spectrum of  $m/z$  310 showed a fragment ion at  $m/z$  266 (loss of  $\text{CO}_2$ ), and the  $\text{MS}^3$  fragmentation spectrum of  $m/z$  266 showed a fragment ion at  $m/z$  230 (loss of HCl). The difference in mass between the molecular ion of the product (310 Da) and DCF (294 Da) was 16 Da, which might be related to the hydroxylation of the compound. The addition of a hydroxyl to the molecule supported the lower retention time observed for the compound by increasing the molecule's polarity. This byproduct of  $m/z$  310 Da was not identified by Quintana et al. (2010).

Other peaks at 6 and 7.2 min were obtained by LC-MS. A molecular ion at  $m/z$  328 Da and two additional ion fragments at  $m/z$  284 and 248 were revealed in the MS spectrum shown in Fig. 4c. Another molecular ion at  $m/z$  300 Da and one ion fragment at  $m/z$  161 were tentatively identified in the MS spectrum (Fig. 4d). These structures are in agreement with the MS/MS and  $\text{MS}^3$  fragmentations identified and are similar to those observed by Quintana et al. (2010). The difference in mass between the

compound at  $m/z$  328 Da and DCF at  $m/z$  294 Da (Fig. 4c) correspond to a chlorine (34 Da), which represent substitution of a hydrogen by a chlorine atom on DCF. The product ion at  $m/z$  300 Da (Fig. 4d) is believed to have been formed through a lactone intermediate by the decarboxylation and oxidation of the dichlorinated ring at position 4, following a mechanism similar to that described by Miyamoto et al. (1997) in the metabolic HClO oxidation of DCF. Conversely, no  $\text{CO}_2$  loss was observed for the  $m/z$  328 Da ion (i.e., there was no carboxylic acid group in the structure). However, there was a CO loss (typical for alcohols) and a fragment at  $m/z$  161 Da, corresponding to the dichlorinated phenolate anion ( $\text{C}_6\text{H}_3\text{OCl}_2$ ), the resulting product was hydroxylated at position 4 of the dichlorinated benzene ring. The investigation of the (eco)toxicological effects of these byproducts and DCF in drinking water in future research is thus required.

The reaction of chlorine with organic compounds occurs mainly by addition and substitution, usually at hydrogen positions. The oxidation with chlorine occurs primarily at sites rich in electrons, such as in unsaturated compounds (double or triple bonds) and in aromatic rings activated with hydroxyl groups and amines (Bedding et al., 1983).

The GAC was qualitatively efficient in removing DCF, as indicated by zero absorbance at 278 nm ( $\lambda$  max DCF) and low concentrations of DOC, and no DCF was detected in the chromatogram obtained by HPLC-DAD (Table 1 and Fig. 1a). Because the LOQ of the method was  $3 \mu\text{g L}^{-1}$ , the removal of DCF in GAC was greater than or equal to 99.7%.

### 3.1.2. Conventional treatment with pre-oxidation (chlorine and chlorine dioxide) followed by CAG filtration

The absorbance values at 254 and 278 nm and the DOC of both sand-filtered water (for both pre-oxidants) and synthetic water

(Table 1) were nearly identical, indicating the poor efficiency of these treatment steps in the removal of AHS and DCF.

Because the measured concentration of DCF in the synthetic water was  $1013 \mu\text{g L}^{-1}$ , the DCF removal was approximately 15% after pre-oxidation with chlorine ( $1 \text{ mg Cl}_2 \text{ L}^{-1}/1 \text{ h}$ ), coagulation, flocculation, sedimentation and sand filtration. When the pre-oxidation was performed with chlorine dioxide ( $0.25 \text{ ClO}_2 \text{ mg L}^{-1}/30 \text{ min}$ ), the DCF removal was approximately 25% (Table 1 and Fig. 3). Thus, chlorine dioxide was more effective than chlorine in removing DCF. However, to efficiently remove DCF from synthetic water, it would be necessary to use a higher dose of oxidant and longer contact time. This was not done to not exceed the limits of residual oxidant and chlorite established by regulatory agencies and also due to the possible interference of these compounds during the adsorption of DCF on GAC.

Fig. 1b shows the overlapped chromatograms obtained by HPLC–DAD of the synthetic water, sand-filtered water (after conventional treatment with pre-oxidation with chlorine), water filtered on GAC and after disinfection of the water filtered on GAC. A reduction in the height of the chromatographic peak for DCF in the sand-filtered water in comparison with the synthetic water and possible formation of byproducts of DCF due to chlorine oxidation were observed. These byproducts were observed as peaks in the chromatogram at approximately 4 min and between 5.5 and 6.5 min.

As shown in Figs. 1b, c and 3, DCF was not detected (up to  $2 \mu\text{g L}^{-1}$ ) in the water after GAC filtration (pre-treatment with both pre-oxidants) and after disinfection of GAC-filtered water, demonstrating that the GAC used was effective in the removal of DCF ( $\geq 99.7\%$ ). Other indications of the absence of DCF after GAC filtration were the zero absorbance at 278 nm and low concentrations of DOC (Table 1).

Fig. 1c shows a minor peak area for DCF was observed in the sand-filtered water in comparison with the synthetic water (pre-oxidized with chlorine dioxide). Nevertheless, the presence of a peak near at 4 min was clear, indicating the presence of a byproduct. A byproduct with a molecular ion of  $m/z$  310 Da ( $\text{C}_{14}\text{H}_9\text{O}_3\text{NCl}_2$ ) was identified by LC–MS/MS (Fig. 4b), representing the introduction of an oxygen atom and the loss of two hydrogen atoms. Fragment ions at  $m/z$  266 ( $\text{C}_{13}\text{H}_9\text{OCl}_2\text{N}$ ) for the loss of  $\text{CO}_2$  and at  $m/z$  230 ( $\text{C}_{13}\text{H}_8\text{OClN}$ ) for the loss of HCl were also observed. The byproduct of  $m/z$  310 Da corresponded to the addition of a hydroxyl to the nonchlorinated ring of DCF (Fig. 4b).

Chlorine dioxide has a lower oxidation potential than that of ozone and a greater potential than the potentials of chlorine and chloramines (Huber et al., 2005). Oxidant alternatives to chlorine, such as chlorine dioxide, are indicated when there is a high concentration of precursors (DOM, algae, bromides and cyanobacteria) to avoid the formation of halogenated byproducts in water, such trihalomethanes (Muttamara et al., 1995).

However, chlorine dioxide can produce aldehydes and carboxylic acids in the presence of DOM (Dąbrowska et al., 2005), as well as inorganic byproducts, such as chlorite and chlorate, which are considered harmful to human health (Steffen and Wetzel, 1993). With respect to organic compounds, chlorine dioxide presents a strong reactivity for phenols, neutral tertiary amines and certain polyaromatic compounds (Hoigné and Bader, 1994).

In most cases, the use of chlorine and chlorine dioxide oxidants does not promote the complete mineralization of pharmaceuticals to  $\text{CO}_2$ , but leads the formation of a wide variety of byproducts (Melo et al., 2009).

#### 4. Conclusions

Under the optimal conditions for the removal of turbidity and color, the conventional treatment comprising coagulation with alumi-

num sulfate ( $3.46 \text{ mg L}^{-1}$  of aluminum and pH 6.50), flocculation, sedimentation and sand filtration did not remove DCF.

In the pre-oxidation with chlorine ( $\text{Cl}_2 \text{ mg L}^{-1}/1 \text{ h}$ ) followed by coagulation, flocculation, sedimentation and sand filtration approximately 15% of DCF removal was obtained, whereas with chlorine dioxide oxidant ( $\text{ClO}_2$   $0.25 \text{ mg L}^{-1}/30 \text{ min}$ ) the removal was approximately 25%. Comparing the two pre-oxidants, chlorine dioxide was considered the stronger oxidant and was more effective than chlorine in reducing DCF.

In the disinfection (chlorination) of sand-filtered water (conventional treatment without pre-oxidation), DCF was reduced by approximately 35 and 97% for contact times of 30 min and 24 h, respectively. Under the studied conditions, chlorine was shown to be an effective oxidant in the removal of DCF. However, because the concentration of DOC obtained was approximately the same as that in the synthetic water, the mineralization of DCF was incomplete and byproducts were formed.

Among the stages of treatment studied, adsorption on GAC resulted in the most significant removal of DCF. Accordingly, DCF was not detected in water samples after this stage ( $\text{LOD} = 2 \mu\text{g L}^{-1}$ ). Considering that the LOQ of the method was  $3 \mu\text{g L}^{-1}$ , at least 99.7% of the DCF was removed by GAC. Because the rupture curves of GAC were not studied, the results of GAC can be considered qualitative. However, to investigate the removal of DCF in field-scale water treatment plants, the method must be improved to achieve lower detection limit (of approximately  $\text{ng L}^{-1}$ ).

In the oxidation with chlorine, three byproducts were tentatively identified, corresponding to a hydroxylation, aromatic substitution of one hydrogen by chlorine and a decarboxylation/hydroxylation. The oxidation with chlorine dioxide resulted in only one byproduct (hydroxylation).

The results of this study have confirmed the need to better understand the identification, occurrence and fate of byproducts of pharmaceuticals formed during drinking water treatment and evaluate their (eco)toxicological effects. Also future studies on the removal of pharmaceuticals by conventional processes combined with non-conventional processes, such as GAC filtration, ozonation, nanofiltration and oxidative processes must be performed.

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#### Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.chemosphere.2013.03.010>.

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