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2 **Second-order advantage with excitation-emission**  
3 **photoinduced fluorimetry for the determination of the**  
4 **antiepileptic carbamazepine in environmental waters**

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## 21 **Abstract**

22 A photochemically-induced fluorescence system combined with second-order chemometric  
23 analysis for the determination of the anticonvulsant carbamazepine (CBZ) is presented. CBZ  
24 is a widely used drug for the treatment of epilepsy and is included in the group of emerging  
25 contaminant present in the aquatic environment. CBZ is not fluorescent in solution but can be  
26 converted into a fluorescent compound through a photochemical reaction in a strong acid  
27 medium. The determination is carried out by measuring excitation-emission photoinduced  
28 fluorescence matrices of the products formed upon ultraviolet light irradiation in a laboratory-  
29 constructed reactor constituted by two simple 4 W germicidal tubes. Working conditions  
30 related to both the reaction medium and the photoreactor geometry are optimized by an  
31 experimental design. The developed approach enabled the determination of CBZ at trace  
32 levels without the necessity of applying separation steps, and in the presence of uncalibrated  
33 interferences which also display photoinduced fluorescence and may be potentially present in  
34 the investigated samples. Different second-order algorithms were tested and successful  
35 resolution was achieved using multivariate curve resolution-alternating least-squares (MCR-  
36 ALS). The study is employed for the discussion of the scopes and yields of each of the  
37 applied second-order chemometric tools. The quality of the proposed method is probed  
38 through the determination of the studied emerging pollutant in both environmental and  
39 drinking water samples. After a pre-concentration step on a C18 membrane using 50.0 mL of  
40 real water samples, a prediction relative error of 2 % and limits of detection and  
41 quantification of 0.2 and 0.6 ng mL<sup>-1</sup> were respectively obtained.

42

43 *Keywords:*

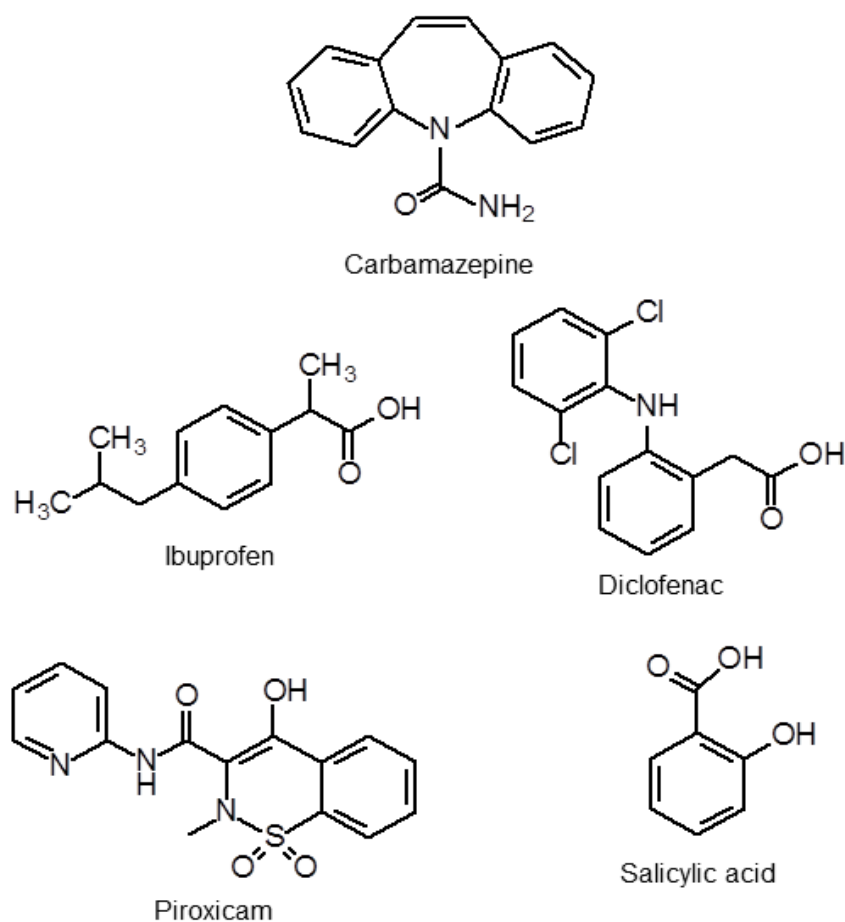
44 Photoinduced fluorescence

45 Multivariate calibration

46 Carbamazepine

47 **1. Introduction**

48 Carbamazepine (CBZ), 5H-dibenzo[*b,f*]azepine-5-carboxamide (Fig. 1) is an  
49 anticonvulsant drug widely used for the treatment of epilepsy and psychiatric diseases [1],  
50 and is included in the group of emerging contaminants [2]. This pharmaceutical pollutant is  
51 of particular concern because of its important toxicological and pharmacological effects in  
52 mammals, humans and the aquatic environment [3–6], in addition to the harmful  
53 consequences produced by its major photoproduct, acridine [7,8].



54

55 **Fig. 1** Structure of carbamazepine and potential interferences.

56

57 Environmental studies have demonstrated that CBZ is one of the most frequently detected  
58 pharmaceutical in sewage-treatment plant effluents, river water and drinking water [9,10]. A

59 field study of occurrence and fate of CBZ and other five pharmaceuticals in surface waters of  
60 Switzerland concluded that CBZ reached concentrations of 0.4 and 0.95 ng mL<sup>-1</sup> in river and  
61 wastewater treatment plant effluents, respectively [11]. An European Union (EU) monitoring  
62 study for organic compounds in rivers and streams across Europe indicated that CBZ is one  
63 of the most frequently detected compound (95%), with an average concentration of 0.25 ng  
64 mL<sup>-1</sup> and maximum concentrations of about 11 ng mL<sup>-1</sup> [12]. A recent study related to the  
65 occurrence of polar organic pollutants in EU ground waters included CBZ in the list of most  
66 frequently found pharmaceuticals (42.1 %), with a maximum concentration of 0.39 ng mL<sup>-1</sup>  
67 [13].

68 CBZ seems to be persistent in the environment, therefore qualifying as a suitable marker  
69 for anthropogenic influences on the aquatic environment [14]. The determination of CBZ and  
70 atrazine was employed as a target analysis for tracers of organic contamination in drinking  
71 and surface waters, resulting in a useful tool to prioritize samples which should be further  
72 screened for suspect contaminants [15].

73 Very recently, during the analysis of selected pharmaceuticals in fish and surface waters  
74 directly affected by irrigation with reclaimed water, CBZ was consistently detected, with a  
75 significant bioaccumulation factor in mosquito fish [16].

76 Chromatographic methods are the most commonly applied ones for the determination of  
77 CBZ or its photodegradation products in different matrices [9–39], although  
78 spectrophotometric, mass spectrometric, electrochemical and capillary electrophoretic  
79 methods have also been proposed [40–47]. Since CBZ is not fluorescent in solution,  
80 fluorimetric methods for its determination have been developed in a nylon surface [48] or  
81 through the formation of fluorescent derivatives by oxidation with Ce(IV) [49,50],  
82 permanganate [51] and lead dioxide [52], or by photochemical reaction [53].

83 The determination of contaminants in complex samples brings the problem of the presence  
84 of interfering agents which must be removed, extending the analysis time and the  
85 experimental work. On the other hand, these separative steps frequently involve the use of  
86 organic solvents which are harmful to health and pollute the environment. In this regard, with  
87 the purpose of contributing with the protection of the environment and decreasing the health  
88 impact, there is a particular interest in developing methods for analytes of ecological concern  
89 complying with the principles of green analytical chemistry [54,55].

90 In this paper, we present a new and safe photochemically-induced fluorescence system  
91 for the determination of CBZ in environmental water samples without involving organic  
92 solvents. An acidic solution of CBZ is irradiated with two germicidal UV lamps, and the  
93 concentration of the formed photoproducts is then spectrofluorimetrically determined in the  
94 presence of pharmaceuticals (or their photoproducts) usually detected in the aquatic  
95 environment, coupling excitation-emission photoinduced fluorescence matrices (EEPIFMs)  
96 to multivariate calibration. Four chemometric algorithms which achieve the second order  
97 advantage, namely, parallel factor analysis (PARAFAC) [56] unfolded partial least-squares  
98 coupled to residual bilinearization (U-PLS/RBL) [57,58], multidimensional partial least-  
99 squares [59] coupled to residual bilinearization (N-PLS/RBL), and multivariate curve  
100 resolution-alternating least-squares (MCR-ALS) [60] were applied to process the EEPIFMs.  
101 Second-order advantage refers the capacity of certain second-order algorithms to predict  
102 concentrations of sample components in the presence of any number of unsuspected  
103 constituents [61,62]. Notable differences in the prediction capabilities of the employed  
104 algorithms were observed and discussed, and the feasibility of determining CBZ in natural  
105 water samples is demonstrated.

106

## 107 **2. Experimental**

108

### 109 *2.1. Reagents and solutions*

110

111 CBZ was obtained from Sigma (St. Louis, MO, USA). Methanol and hydrochloric acid  
112 were purchased from Merck (Darmstadt, Germany). Compounds tested as potential  
113 interferences were of analytical grade and were used as received. The stock solution of CBZ  
114 ( $530 \mu\text{g mL}^{-1}$ ) was prepared in methanol. From this solution, more diluted aqueous working  
115 solutions were obtained. Ultrapure Milli-Q water was used throughout the work.

116

### 117 *2.2. Instrumentation*

118

119 Fluorescence spectra were measured using an Aminco Bowman (Rochester, NY, USA)  
120 Series 2 luminescence spectrometer equipped with a 150 W xenon lamp. These spectra were  
121 obtained using excitation and emission wavelengths of 308 and 410 nm, respectively, and  
122 both the excitation and emission slit widths were of 8 nm using 1.00 cm quartz cells. The  
123 photomultiplier tube (PMT) sensitivity was fixed at 700 V and the temperature of the cell  
124 compartment was kept constant at 20 °C by circulating water from a thermostated bath  
125 (Cole-Parmer, Illinois, USA).

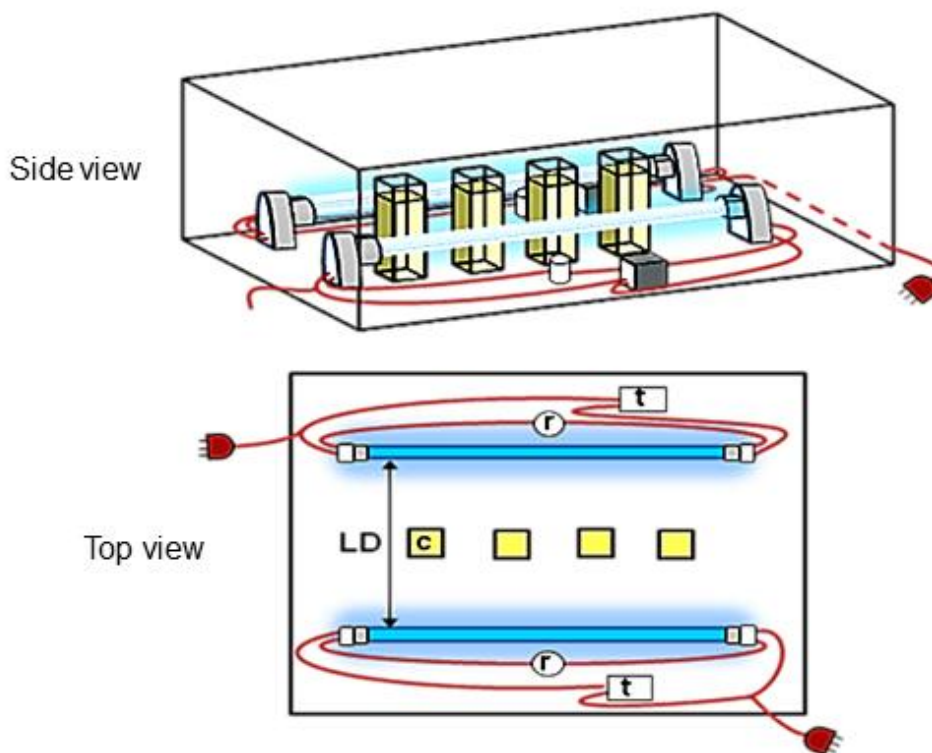
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### 127 *2.3. Procedure*

128

129 The photodegradation reaction was carried out in a very simple reactor constructed in our  
130 laboratory, constituted by two germicidal tubes of 4 W (Fig. 2). Both the geometry of the  
131 photoreactor and the experimental conditions to reach the best signal were optimized (see

132 below). EEPiFMs were measured from 280 to 320 nm (each 2 nm) and from 380 to 450 nm  
133 (each 1 nm), respectively, and were then subjected to second-order data analysis.



134  
135 **Fig. 2** Photoreactor. LD = distance between the lamps, C = quartz cells, r = reactance, t =  
136 transformer.

137  
138 *2.4. Optimization of the parameters affecting the fluorescence signal*

139  
140 A five-level central composite design of 17 experiments was applied for investigating the  
141 influence of the three variables on the fluorescence intensity, with three replicates at the  
142 central point. These variables were the concentration of hydrochloric acid ( $C_{HCl}$ ), the  
143 irradiation time (IT) and the distance between the lamps (LD). The fluorescence intensity was  
144 recorded for each solution using 308 and 410 nm as excitation and emission wavelengths

145 respectively. The runs were carried out in a randomized sequence to minimize the effect of  
 146 uncontrolled variables on the response. The resulting experimental matrix is detailed in Table  
 147 1, and the quadratic regression model selected to define the relationship between the response  
 148 and the variables was:

$$F = b_0 + \sum_{i=1}^3 b_i x_i + \sum_{i=1}^3 b_{ii} x_i^2 + \sum_{i=1}^3 \sum_{j=i+1}^3 b_{ij} x_i x_j + e \quad (1)$$

150  
 151 where  $F$  is the response,  $x_i$  and  $x_j$  are the studied factors,  $b_0$ ,  $b_i$ ,  $b_{ii}$  and  $b_{ij}$  are the intercept,  
 152 linear, quadratic and interaction coefficients, and  $e$  the model error.

153

**Table 1**  
 Design generated for a central composite design and the obtained response values.

Run	$b_1$ - $C_{HCl}/M$	$b_2$ -IT/min	$b_3$ -LD/cm	$F$ (response)
1	1.50	1.00	6.00	5.8
2	1.50	30.00	6.00	24.7
3	2.50	7.00	8.00	16.7
4	3.00	16.00	6.00	32.6
5	2.50	25.00	3.50	25.4
6	0.30	16.00	6.00	14
7	1.50	16.00	10.00	26.5
8	1.50	16.00	6.00	31.8
9	0.50	7.00	8.00	15.4
10	0.50	25.00	3.50	6.4
11	0.50	25.00	8.00	21.8
12	1.50	16.00	6.00	33.6
13	2.50	25.00	8.00	29.2
14	1.50	16.00	2.00	23.6
15	1.50	16.00	6.00	33.7
16	2.50	7.00	3.50	24.7
17	0.50	7.00	3.50	6.3

$C_{HCl}$ : concentration of hydrochloric acid; IT: irradiation time; LD: distance between the lamps.

154



155 2.5. *Quantitative analysis*

156

157 Preliminary experiments indicated that, under the established working conditions, linearity  
158 is held until  $61 \text{ ng mL}^{-1}$ , which was the limiting assayed concentration in subsequent  
159 analyses.

160 A calibration set of 9 samples was prepared, by duplicate, measuring appropriate aliquots  
161 of stock solution of CBZ into 2.00 mL calibrated flasks, evaporating the solvent with nitrogen  
162 and completing to the mark with  $2 \text{ mol L}^{-1}$  HCl. A validation set was similarly prepared  
163 employing concentrations different from those used for calibration and following a random  
164 design. With the purpose of evaluating the proposed strategy in the presence of these  
165 interferent agents, twenty additional test samples containing random concentrations of CBZ  
166 and these foreign compounds were prepared. The interferents were evaluated at the following  
167 concentration ranges: 0–5600, 0–1200, 1–9, and 0–5000  $\text{ng mL}^{-1}$  for ibuprofen, diclofenac,  
168 piroxicam, and salicylic acid, respectively. The maximum level of each evaluated  
169 interference was selected in order to avoid the saturation of the fluorescence signal. Taking  
170 into account that the highest CBZ concentration was about  $60 \text{ ng mL}^{-1}$ , with the exception of  
171 piroxicam, each interferent agent was between 16 and 90 times more concentrated than the  
172 analyte.

173

174 2.6. *Real water samples*

175

176 All investigated water samples were prepared by spiking them with CBZ at three different  
177 concentrations, obtaining levels between  $0.4$  and  $5.5 \text{ ng mL}^{-1}$ . Tap water from Rosario city  
178 (Santa Fe, Argentina) and underground water from Funes and Venado Tuerto cities (Santa  
179 Fe, Argentina) samples were used as received. The Paraná River sample was collected near

180 Rosario city, and after spiking it with CBZ, it was filtered through a filter paper to remove  
181 suspended solid materials. In order to improve the sensitivity of water analysis, a solid-phase  
182 extraction (SPE) procedure with C18 membranes was applied. Prior to sample application,  
183 each membrane was conditioned with 500  $\mu\text{L}$  of methanol. Positive pressure was used to  
184 force the water sample through the membrane. For concentrations of CBZ at sub-part-per-  
185 billion levels, 50.0 mL of sample was employed, while a volume of 10.0 mL was used for the  
186 remaining samples. Following the extraction, the disk was dried by forcing air through it  
187 using a 25 mL syringe. Then, the retained CBZ was eluted with 500  $\mu\text{L}$  of methanol and the  
188 liquid was collected in a 2.00 mL volumetric flask. After evaporation of the solvent with  
189 nitrogen, the residue was reconstituted to the mark with 2 mol  $\text{L}^{-1}$  HCl. Thus, the  
190 preconcentration factors were 25 and 5 for samples with sub-part-per-billion and part-per-  
191 billion concentrations, respectively. Then, the procedure described above was performed.

192

### 193 *2.7. Software*

194

195 The experimental design and optimization was carried out using Design Expert 6.0 (Stat-  
196 Ease, Inc.). The employed chemometric algorithms were written in MATLAB 7.6 [63].  
197 PARAFAC, U- and N-PLS/RBL were implemented using the graphical interface of the  
198 MVC2 toolbox, which can be freely downloaded from the webpage [www.iquir-](http://www.iquirconicet.gov.ar/descargas/mvc2.rar)  
199 [conicet.gov.ar/descargas/mvc2.rar](http://www.iquirconicet.gov.ar/descargas/mvc2.rar). MCR-ALS is available in the Internet at  
200 <http://www.mcrals.info/>. Theoretical considerations of the applied algorithms can be found in  
201 the supplementary information.

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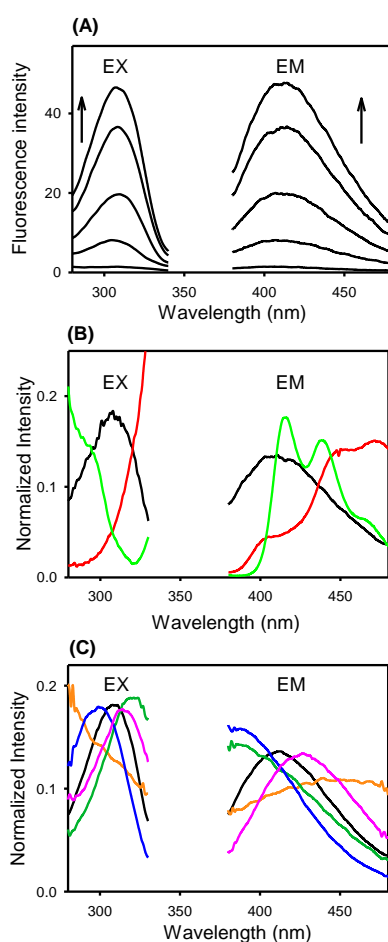
## 203 **3. Results and discussion**

204

205 3.1. Preliminary studies

206

207 As was previously indicated, CBZ does not display native fluorescence, but emission can  
208 be obtained upon UV irradiation under certain working conditions, indicating the formation  
209 of one or more emissive photoproducts (Fig. 3A). In the literature, different CBZ  
210 photoproducts have been reported depending on the employed experimental conditions.



211

212 **Fig. 3** (A) Excitation and emission fluorescence spectra of CBZ photoproducts (initial  $C_{CBZ} =$   
213  $0, 10.1, 25.3, 48.0,$  and  $60.0 \text{ ng mL}^{-1}$ ). (B) Normalized excitation and emission fluorescence  
214 spectra of CBZ photoproducts (black line), acridine (red line) and acridone (light green line).  
215 (C) Normalized excitation and emission fluorescence spectra of CBZ (black line), ibuprofen  
216 (orange line), diclofenac (green line), piroxicam (blue line), and salicylic acid (pink line) after  
217 irradiation under the used experimental condition.

218

219 For example, acridine and acridone were the main identified photoproducts when an acid  
220 solution of CBZ was irradiated with a 1500 W arc xenon lamp during 30 min [64]. CBZ  
221 treatment with UV irradiation (17 W mercury lamp, 254 nm) in the presence of H<sub>2</sub>O<sub>2</sub>  
222 produced acridine, a series of acridine intermediates and small amounts of salicylic acid,  
223 catechol and anthranilic acid among the reaction products [65]. Chiron et al. studied the  
224 photodegradation of CBZ in artificial estuarine water, mimicking natural processes [7]. After  
225 evaluating different experimental conditions, it was concluded that besides acridine (the  
226 major photodegradation intermediate), 10-hydroxycarbamazepine, hydroxyacridine-9-  
227 carboxaldehyde, and acridone are also formed.

228 Under our working conditions, the obtained wide spectra with excitation and emission  
229 maxima at 308 and 410 nm respectively, do not suggest a significant contribution of either  
230 acridine or acridone (Fig. 3B). However, regardless of the nature of the formed  
231 photoproducts, a linear relationship between the CBZ concentration and the obtained  
232 fluorescence intensity was corroborated and, therefore, a quantitative analysis could be  
233 properly developed.

234

### 235 *3.2. Optimization of the experimental conditions*

236

237 Exploratory experiments showed that the type and concentration of acid used in the  
238 reaction medium, the time of sample irradiation and the distance between the reactor lamps  
239 (the sample is positioned equidistant between both lamps) had critical effects on the  
240 photochemically induced fluorescence. Although in some systems the presence of different  
241 organized media could sensitize photochemical reactions [66,67], in our working conditions  
242 selected surfactants (sodium dodecyl sulfate, hexadecyltrimethylammonium bromide, Triton  
243 X-100) and cyclodextrins ( $\beta$ -,  $\gamma$ -,  $\alpha$ - and 2-hydroxy-propyl- $\beta$  cyclodextrins) did not produce a

244 significant signal improvement. On the other hand, desoxygenation of the medium with a flow  
245 of nitrogen did not improve the signal intensity.

246 As regards the acid employed, nitric, sulfuric and hydrochloric acids were checked. In the  
247 presence of nitric acid, signals were not detected, and the sulfuric acid background signal was  
248 significant. Hydrochloric acid produced the best signals and, therefore, it was selected for the  
249 subsequent experiments.

250 It was found that irradiation with two 4 W lamps, rather than using either one 4 W lamp or  
251 8 W lamps, produced an efficient photodegradation reaction of CBZ. Besides, the distance  
252 between these lamps and the time of irradiation modified the signal. These factors were  
253 optimized using a surface response methodology. Table 2 displays the ANOVA results for  
254 the selected quadratic model, where it can be appreciated that the variables explain the data  
255 and indicate that the variable effect is significant at 95 % confidence level. The coefficients  
256 estimated for the mathematical model in terms of actual factors were:  $-40$ ,  $31$ ,  $2.3$ ,  $6.9$ ,  $-5.2$ ,  
257  $-0.08$ ,  $-0.48$ ,  $-1.5$  for intercept,  $C_{\text{HCl}}$ , IT, LD,  $(C_{\text{HCl}})^2$ ,  $(\text{IT})^2$ ,  $(\text{LD})^2$ ,  $C_{\text{HCl}} \times \text{LD}$  and  $\text{IT} \times \text{LD}$ ,  
258 respectively.

259 The optimum values obtained for  $C_{\text{HCl}}$ , IT and LD were  $2 \text{ mol L}^{-1}$ , 20 min and 6 cm,  
260 respectively. These conditions were used for the corresponding quantitative analysis.

261 It is important to point out that the geometry of the photoreactor (Fig. 2) allows the  
262 simultaneous irradiation of four solutions contained in the quartz cells. Thus, the time of  
263 irradiation is equivalent to 5 minutes per sample.

264

### 265 3.3. Quantitative analysis

266

267 The purpose of the present work is to determine CBZ in natural matrices where other  
268 concomitantly present compounds are potentially able to produce interference through either

269 themselves or their fluorescent photoproducts when the sample is subjected to the irradiation  
 270 protocol. Therefore, different pharmaceuticals selected from the list of organic  
 271

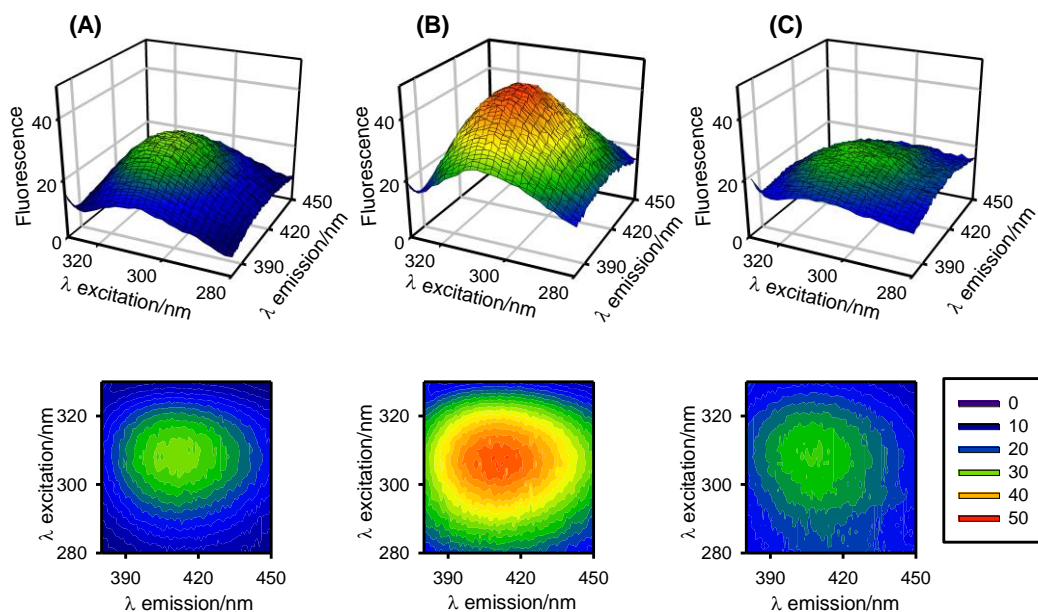
**Table 2**  
 Analysis of variance (ANOVA) for the selected quadratic model.<sup>a</sup>

Source	Sum of squares	DF	Mean square	F value	<i>p</i> > F
Model	1408.40	8	176.05	23.46	< 0.0001
<i>b</i> <sub>1</sub> -C <sub>HCl</sub>	511.89	1	511.89	68.22	< 0.0001
<i>b</i> <sub>2</sub> -IT	151.89	1	151.89	20.24	0.020
<i>b</i> <sub>3</sub> -LD	58.01	1	58.01	7.73	0.0239
<i>b</i> <sub>11</sub>	179.14	1	179.14	23.87	0.0012
<i>b</i> <sub>22</sub>	464.96	1	464.96	61.978	<0.0001
<i>b</i> <sub>33</sub>	88.71	1	88.71	11.82	0.0088
<i>b</i> <sub>13</sub>	97.37	1	97.37	12.98	0.0070
<i>b</i> <sub>23</sub>	45.05	1	45.05	6.00	0.0399
Lack of Fit					0.100

<sup>a</sup> The term *b*<sub>12</sub> was not significant (*p* > 0.05) and was excluded of the analysis. DF = degree of freedom; *p* = probability; *R*<sup>2</sup> (coefficient of determination) = 0.959; Pred *R*<sup>2</sup> (measures how well the model will predict the responses for a new experiment) = 0.794; Adeq precision (measures the signal to noise ratio) = 13.97.

272  
 273 micropollutants usually detected in the aquatic environment were checked as potential  
 274 interferents, namely ibuprofen, diclofenac, piroxicam, salicylic acid, naproxen, ketoprofen  
 275 and atenolol [11,68]. We found that, after irradiation, the excitation and emission spectra of  
 276 the photoproducts of the first four compounds (Fig. 1) are significantly overlapped with those  
 277 corresponding to CBZ ones, producing a severe interference (Fig. 3C). Thus, for improving  
 278 the selectivity of the method, a second-order calibration applying algorithms which achieve  
 279 the so-called second-order advantage was proposed.

280



281

282 **Fig. 4** Three-dimensional plots and the corresponding contour plots of excitation-emission  
 283 photofluorescence matrices for (A) a validation sample containing  $48.0 \text{ ng mL}^{-1}$   
 284 CBZ, (B) a test sample containing  $56.0 \text{ ng mL}^{-1}$  CBZ,  $2000 \text{ ng mL}^{-1}$  ibuprofen,  $1500 \text{ ng}$   
 285  $\text{mL}^{-1}$  salicylic acid,  $600 \text{ ng mL}^{-1}$  diclofenac and  $2 \text{ ng mL}^{-1}$  piroxicam, and (C) a spiked river  
 286 sample after solid-phase extraction (original  $C_{\text{CBZ}} = 5.5 \text{ ng mL}^{-1}$ ).  
 287

288 Firstly, EEPFMs of CBZ photoproducts under optimal working conditions were recorded  
 289 for calibration and validation samples (Fig. 4A), where only the studied analyte is present.

290 These matrices were successfully resolved by usual second-order algorithms such as  
 291 PARAFAC, U-PLS, N-PLS and MCR-ALS (data not shown). However, the results were  
 292 different when test samples containing interferent agents were processed. Fig. 4B shows the  
 293 three-dimensional plot of the EEPFM for a typical sample with interferences and the  
 294 corresponding contour plot. The results obtained with different algorithms applied to these  
 295 samples are discussed below.

296

### 297 3.3.1. PARAFAC

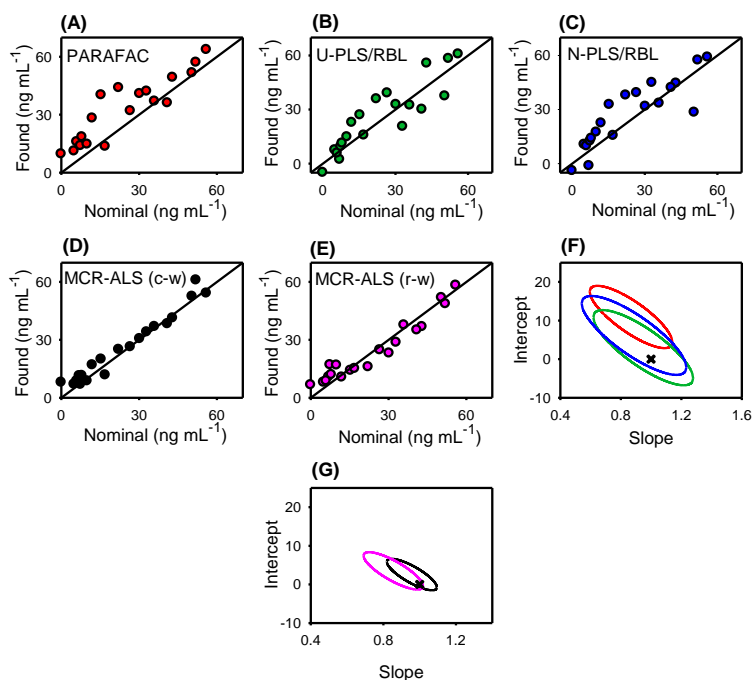
298

299 The PARAFAC model allowed us to obtain physically interpretable profiles. The  
300 identification of the analyte was done with the aid of the estimated excitation and emission  
301 profiles, and comparing them with those for an irradiated standard CBZ solution. The number  
302 of components was selected by the so-called core consistency analysis [69], which consists in  
303 studying the structural model based on the data and the estimated parameters of gradually  
304 augmented models. A PARAFAC model is considered to be appropriate if incorporating an  
305 additional component does not improve the fit considerably [69]. The number of components  
306 also was analysed through the spectral profiles produced by the addition of a new component.  
307 If this addition generated repeated profiles, suggesting overfitting, this new component was  
308 discarded. The number of responsive components obtained using both procedures was two in  
309 validation samples and three in samples with interferents. In validation samples, the obtained  
310 number of components could be justified taking into account the presence of two different  
311 signals corresponding to CBZ and background signals. On the other hand, in test samples  
312 interferences are extracted as a single signal.

313 PARAFAC was initialized with the loadings giving the best fit after a small number of  
314 trial runs, selected from the comparison of the results provided by generalized rank  
315 annihilation and several random loadings [70].

316 Fig. 5A shows the prediction results corresponding to the application of PARAFAC to the  
317 20 samples with interferents. As can be appreciated, the results are rather poor. This fact may  
318 be explained considering the significant spectral overlapping among the analyte and  
319 interferences, which precludes the successful decomposition of the second-order data [71].  
320 The elliptical joint confidence region (EJCR, [72]) test for the slope and intercept of the  
321 found vs. nominal concentrations plot shows that the ideal point (1,0) lies outside the EJCR  
322 surface (Fig. 5F), also suggesting that PARAFAC is inappropriate for resolving the system  
323 under investigation.





325

326 **Fig. 5** Plots for CBZ predicted concentrations in samples with interferences (test samples) as  
 327 a function of the nominal values using (A) PARAFAC, (B) U-PLS/RBL, (C) N-PLS/RBL,  
 328 (D) MCR-ALS (column-wise augmentation), and (E) MCR-ALS (row-wise augmentation).  
 329 Solid lines indicate the perfect fits. (F) Elliptical joint regions (at 95 % confidence level)  
 330 for slope and intercept of the regression of PARAFAC (red line), U-PLS/RBL (green line), and  
 331 N-PLS/RBL (blue line). (G) Elliptical joint regions (at 95 % confidence level) for slope and  
 332 intercept of the regression of MCR-ALS using column-wise (black line) and row-wise (pink  
 333 line) augmentations. Crosses in (F) and (G) mark the theoretical (intercept = 0, slope = 1)  
 334 point.

335

### 336 3.3.2. U- and N-PLS

337

338 In the cases of U- and N-PLS/RBL, the optimum number of factors for the calibration set  
 339 applying the cross-validation method described by Haaland and Thomas [73] was also two.  
 340 When these algorithms were applied to samples containing interferences, in addition to the  
 341 latent variables estimated from the calibration set, they required the introduction of the RBL  
 342 procedure with an additional number of components corresponding to the unexpected sample  
 343 constituents. This number, estimated by suitable consideration of RBL residues [74], ranged

344 from 1 to 2. Adding more unexpected components did not improve the fit. Apparently,  
345 PLS/RBL considers the profiles of the four interferences as additional one or two  
346 components, and is able to distinguish these combined signals from those of the analyte and  
347 the blank. Figs. 5B and 5C show the prediction results corresponding to the application of U-  
348 PLS/RBL and N-PLS/RBL to the samples containing interferences. In these figures, some  
349 dispersion of the predictions with respect to the perfect fit lines is verified. While the  
350 corresponding ellipses include the theoretical (1,0) point (Fig. 5F), they show large (and  
351 undesirable) sizes. However, although these algorithms have some difficulty to solve the  
352 system under study, they are more flexible and render better results than PARAFAC.

353

### 354 3.3.3. MCR-ALS

355

356 The MCR-ALS model decomposes an augmented data matrix, built by placing matrices  
357 for different samples adjacent to each other, in such a way that the augmentation mode is the  
358 one affected by the profile overlapping. As a result, the poor selectivity in the affected  
359 dimension is recovered in the augmented dimension. In the present system, since a significant  
360 overlapping between analyte and interferences is observed in the excitation and emission  
361 spectra, both modes of augmentation were checked. Therefore, two different data processing  
362 were performed: one of them comprised the building of augmented column-wise (emission  
363 spectral) data matrices containing the test sample data and the calibration data matrices, and  
364 the other one comprised the building of augmented row-wise (excitation spectral) data  
365 matrices, also containing the test and calibration data matrices.

366 Before starting resolution, the determination of the number of MCR components was  
367 estimated by applying singular value decomposition (SVD). Usually, the plot of singular  
368 values as a function of principal component number is visually inspected, locating a number

369 for which the plot stabilizes. This number is initially employed for MCR-ALS analysis, and is  
370 afterwards refined (increased or decreased) until an appropriate solution is found, with a  
371 reasonable least-squares fit and physically recognizable profiles. Given the number of  
372 responsive components, their spectra were then obtained from the analysis of the so-called  
373 “purest” spectra, based on the SIMPLISMA methodology, a multivariate curve resolution  
374 algorithm which extracts the purest spectra of the mixture from a series of spectra of mixtures  
375 of varying composition [75]. The spectra provided by SIMPLISMA were suitable to perform  
376 the resolution and, therefore, it was not necessary to include reference spectra for the analyte  
377 as initial estimates for MCR-ALS. In the present system, the number of MCR components in  
378 both augmentation modes was three. Apparently, the algorithm combines the signals of  
379 interferences but perfectly distinguishes them from those belonging to the analyte and, as will  
380 be shown below, yields very good predictions.

381 During the iterative procedure leading to chemically recognizable solutions the constraint  
382 of non-negativity in both data modes was applied. The selected MCR convergence criterion  
383 was 0.1% (relative change in fit for successive iterations) and the maximum number of  
384 iterations was set to 1000. Convergence was achieved after less than 300 iterations in most of  
385 the evaluated samples. Further, the quality of the MCR-ALS recovered spectral profiles was  
386 evaluated using the criterion of similarity which involves a comparison, through the  
387 correlation coefficient ( $R$ ) between the reference and evaluated spectrum [76]. The value of  $R$   
388 found for CBZ photoproducts in the excitation and emission spectra were 0.9992 and 0.9997,  
389 respectively, corroborating the excellent quality of the MCR-ALS obtained results.

390 Figs. 5D and 5E show the prediction results corresponding to the application of MCR-  
391 ALS to the same test samples described above using the column and row-wise augmentation  
392 respectively. As can be observed, in both cases the predictions are in good agreement with  
393 the corresponding nominal values, with the results of column-wise augmentation being

394 slightly better. This fact could be ascribed to the better selectivity achieved through the  
 395 excitation spectra. The EJCR test (Fig. 5G) corroborates that both ellipses have a small size  
 396 and include the theoretically expected values of (1,0), demonstrating the accuracy of the used  
 397 methodologies.

398 The statistical results are complemented with the values shown in Table 3. The relative  
 399 error of prediction indicates acceptable precision, and both the limit of detection (LOD) and  
 400 limit of quantification (LOQ) obtained are suitable, taking into account that a very simple  
 401 methodology is applied to a complex multicomponent system.

**Table 3**

Statistical results for CBZ using the proposed methodology and MCR-ALS (column-wise augmentation).

	Test samples <sup>a</sup>	Real water samples <sup>b</sup>	Real water samples <sup>c</sup>
LOD <sup>d</sup> (ng mL <sup>-1</sup> )	5	1	0.2
LOQ <sup>e</sup> (ng mL <sup>-1</sup> )	15	3	0.6
RMSEP <sup>f</sup> (ng mL <sup>-1</sup> )	4	0.4	0.1
REP <sup>g</sup> (%)	13	7	2

<sup>a</sup> Twenty samples containing ibuprofen, diclofenac, piroxicam, salicylic acid as interferents.

<sup>b</sup> Preconcentration factor = 5 (the results refer to the original water sample before SPE).

<sup>c</sup> Preconcentration factor = 25 (the results refer to the original water sample before SPE).

<sup>d</sup> LOD, limit of detection calculated according to ref. 78.

<sup>e</sup> LOQ, limit of quantitation calculated as LOD×(10/3.3).

<sup>f</sup> RMSEP, root-mean-square error of prediction.

<sup>g</sup> REP, relative error of prediction.

402

403

404 The latter two figures of merit have been estimated using the expressions recommended by  
 405 IUPAC for the detection capabilities, which take into account the so-called Type 1 and 2  
 406 errors (false detects and false non-detects respectively) [77]. They were applied to the  
 407 pseudo-univariate calibration plot (analyte scores vs. nominal concentrations) provided by  
 408 MCR-ALS, as previously suggested [78].

409

#### 410 3.4. Real water samples

411

412 With the purpose of evaluating the present method in real samples and demonstrating its  
413 ability of overcoming the interference from background matrices, waters from different  
414 origins were analysed. CBZ is detected in water bodies in a wide range of concentrations,  
415 generally in the order of part- and sub-part-per-billion levels. Therefore, the sensitivity of the  
416 present method was improved using a pre-concentration step by employing C18 membrane-  
417 SPE. At this point, it is necessary to point out that the selection of C18 membranes is based  
418 on our excellent experience with this solid-support as extractor of organic compounds  
419 [79–81]. Although other materials could be used for the extraction procedure, previously  
420 reported experiments performed with different commercial and in-house ion-exchange  
421 polymeric sorbents were not successful for CBZ extraction [82].

422 Fig. 6A shows both the excitation and emission spectra of CBZ photoproducts and the  
423 signal of a typical real water sample after the SPE procedure. As can be seen, the selected  
424 sample (river water) shows intense fluorescence signals in the same region where the CBZ  
425 photoproducts emit, which are ascribed to dissolved organic matter [83]. These overlapping  
426 would preclude the direct measurement of the analyte, but it does not represent a problem  
427 when using second-order approaches. Fig. 4C shows both three-dimensional plot of the  
428 EEPIFM and the corresponding contour plot of real sample of river spiked with CBZ and  
429 treated with C18 membrane.

430 A recovery study was performed by spiking water samples with appropriate amounts of  
431 CBZ, in triplicate, at three different concentration levels, following the treatment indicated in  
432 the experimental section. According to the previous results, MCR-ALS was selected to  
433 resolve these samples, and the outstanding results obtained (Table 4, Fig. 6B) suggest that the  
434 method can overcome the problem of the presence of unexpected interferents from the

435 background of the real samples. Table 3 displays the corresponding figures of merit obtained  
436 for these samples.

437 In comparison with the performances of selected methods for the determination of CBZ in  
438 natural waters (Table 5), limits of detection from  $0.2 \times 10^{-3}$  to  $10 \text{ ng mL}^{-1}$  have been found  
439 using different strategies, all using pre-concentrations procedures and most of them applying  
440 chromatographic (separation) approaches. In the present case, a low limit of detection is  
441 achieved in real samples ( $\text{LOD} = 0.2 \text{ ng mL}^{-1}$ ) applying a non-sophisticated method and  
442 without using organic solvents. Note a solid-phase extraction procedure using a higher  
443 amount of sample ( $> 50 \text{ mL}$ ) allows decrease even more the LOD. Additionally, a sampling  
444 rate of about six samples per hour (including the EEPFIM measuring) makes the method very  
445 advantageous.

446

**Table 4**  
Recovery study of CBZ for spiked water samples.<sup>a</sup>

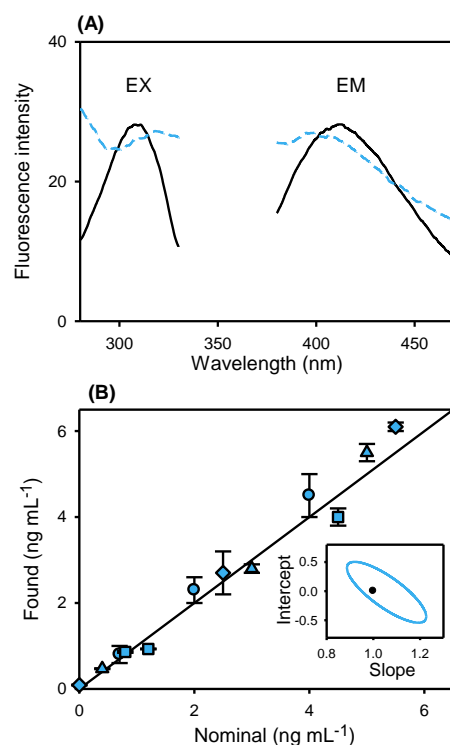
Sample	Taken ( $\text{ng mL}^{-1}$ )	Found ( $\text{ng mL}^{-1}$ ) <sup>b</sup>	Recovery (%)
Underground water (Funes City)	0.70	0.8 (0.2)	114
	2.00	2.3 (0.3)	115
	4.00	4.5 (0.9)	112
Underground water (Venado Tuerto City)	0.40	0.47 (0.01)	117
	3.00	2.8 (0.1)	93
	5.00	5.5 (0.2)	110
Tap water (Rosario City)	0.80	0.86 (0.02)	107
	1.20	0.93 (0.01)	78
	4.50	4.0 (0.2)	89
River water (Paraná River)	0.00	ND <sup>c</sup>	
	2.50	2.7 (0.5)	108
	5.50	6.1 (0.1)	111

<sup>a</sup> using MCR-ALS algorithm (column-wise augmentation).

<sup>b</sup> Mean of three determinations. Standard deviations between parentheses.

<sup>c</sup> ND, not detected.

447



448

449 **Fig. 6** (A) Excitation and emission fluorescence spectra of CBZ photoproducts ( $C_{\text{CBZ}} = 40.0$   
 450  $\text{ng mL}^{-1}$ , black line) and background signals of a river sample without CBZ after the SPE  
 451 treatment (sky-blue dashed line). (B) Plot for MCR-ALS predicted concentrations of CBZ as  
 452 a function of the nominal values in a river (diamonds) and tap water (squares) samples, and in  
 453 two different underground water samples (circles and triangles) spiked analyte (error bars  
 454 correspond to triplicates). The inset shows the corresponding elliptical joint region at 95%  
 455 confidence level. The cross marks the theoretical (intercept = 0, slope = 1) point.  
 456

#### 457 4. Conclusions

458 A novel and simple fluorimetric method for carbamazepine (CBZ) determination was  
 459 developed and successfully applied to the quantitation of this emerging contaminant in water  
 460 samples. Analyses were accomplished in a significant short time, with a minimum operator  
 461 effort and avoiding the use of organic solvents. The selectivity of the method is achieved  
 462 through the coupling of multivariate calibration. Among the different second-order  
 463 algorithms investigated, multivariate curve resolution-alternating least-squares (MCR-ALS)  
 464 showed a superior predictive capability and would be the recommended one in situations  
 465 where interferences present similar profiles as the investigated compound.

**Table 5**

Analytical performance of selected methods reported for the determination of CBZ in natural waters.

Method	VS <sup>a</sup>	Concentration level <sup>b</sup>	RSD <sup>c</sup> and REC <sup>c</sup>	Sample	Ref
SPME-GC-MS	4	LOD = 1.0	RSD = 12.0	GW, SW	[20]
SPE-GC-MS	1000	LOD = $6.5 \times 10^{-3}$ (nanopure water). LOD = $8.7 \times 10^{-3}$ (SW); 0.035–0.060 (lake); 0.030–0.250 (river); 0.100–0.800 (WWTP)	REC = 46–65 (0.100 ng mL <sup>-1</sup> )	SW, STPEs	[21]
SPE-GC-MS	1000	LOD = $9.6 \times 10^{-3}$ ; LODet = $32 \times 10^{-3}$	REC = 80 (TW) and 74 (SW)	TW, SW	[22]
SPE-HPLC-PIF	250	Without SPE: LOD = 30; LOQ = 100. With SPE: 12 (SS with 10 ng mL <sup>-1</sup> added)	RSD = 3.4	STP-WW	[23]
SPE-LC-MS/MS		STPI: 0.369. STPE: 0.426. SW (river): $0.7 \times 10^{-3}$ . SS: 0.100	REC = 83.6–103.5; RSD = 5.9	STPI, STPE, SW	[24]
SPE-GC-MS and SPE-LC-MS/MS	500–1000	MC = 1.2	Absolute REC = 89 (GC) and 99 (LC)	STPEs	[25]
SPE-GC-MS	500	LOD = 2.2; LOQ = 0.074	REC = 67	Municipal STP	[26]
SPE-LC-MS/MS		STPI: 0.356; STPE: 0.251		STPI, STPE, biosolids	[27]
SPE-GC-MS (on-line derivatization)	50–500	LOQ = $8.0 \times 10^{-3}$	REC = 79–108	TW, SW, WWE, GW	[28]
SPE-HPLC-MS	500	LOQ = $1.3 \times 10^{-3}$ (STPE); Found (STPE) = 0.033–1.3	RSD = 0.7 % (10 ng/injected); RSD = 2.88 (100 ng/injected)	Urban WWs	[29]
SPE-HPLC-DAD	500–1000	WWI: LOD = 0.04; LOQ = 0.12. WWE: LOD = 0.02; LOQ = 0.06	REC = 95, RSD = 4.3	WWI, WWE	[30]
SPE-GC-MS	500	LOQ = 0.030	REC = 110; RSD = 11.5	River water	[31]
SPE-LC-MS/MS	100	LOD = 7; LOQ = 19	REC = 88.1 (1 ng mL <sup>-1</sup> ); RSD = 2.2	Hospital WWE	[32]
SPE-LC-MS/MS	100–1000	STPI: LOQ = 0.02; MC = 2. STPE: LOQ = 0.01; MC = 1.9. SW: LOQ = 0.002; MC = 0.081	Absolute REC = 36–98	STPI, STPE, SW, GW, DW	[36]
SPE (MIP)-LC-MS	100	1	REC = 80	WW	[38]
SPE-voltammetry		LOD = 9.4; LOQ = 33. SS: 500	REC = 95.8; RSD = 5.7	WW	[43]
Off- and on-line SPE-LC-QqQ-MS	500	LOD = $0.2 \times 10^{-3}$	RSD < 15	SW and DW	[15]
SPE-LDTD-APCI-MS/MS	100	0.012	RSD = 8	municipal WW	[45]
SPE-EEPIF	10–50	LOD = 1 (PCF = 5); LOD = 0.2 (PCF = 25)	REC = 78–117; REP = 2–7	SW, UW	This work

<sup>a</sup> VS, volume of sample in mL.<sup>b</sup> For comparison, concentration units were unified to ng mL<sup>-1</sup>.<sup>c</sup> Relative standard deviation (RSD) and recovery (REC), both in %.

Abbreviations: APCI, atmospheric pressure chemical ionization; DW, drinking water; EEPIF, excitation-emission photoinduced fluorimetry; GW, groundwater; LC, liquid chromatography; LDTD, laser diode thermal desorption; LOD, limit of detection, LODet, limit of determination, LOQ, limit of quantification; MC, maximum found concentration; MIP, molecularly imprinted polymer; MS, mass spectrometry; MS/MS, tandem mass spectrometry; PCF, preconcentration factor; PIF, photoinduced fluorescence; QqQ, triple quadrupole; REP, relative error of prediction; REC, recovery; RSD, relative standard deviation; SPE, solid-phase extraction; SPME, solid-phase microextraction; SS, spiked sample; STP, sewage treatment plant; STPE, sewage treatment plant effluent; STPI, sewage treatment plant influent; SW, surface water; TW, tap water; UW, underground water; VS, volume of sample; WW, wastewater; WWE, wastewater effluent; WWI, wastewater influent.



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467

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471

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## **Glossary**

*CBZ*: carbamazepine.

$C_{CBZ}$ : concentration of carbamazepine.

$C_{HCl}$ : concentration of hydrochloric acid.

*EPIFMs*: excitation-emission photoinduced fluorescence matrices.

*EJCR*: elliptical joint confidence region.

*EU*: European Union.

*IT*: irradiation time.

*LD*: distance between the lamps.

*LOD*: limit of detection.

*LOQ*: limit of quantification.

*MCR-ALS*: multivariate curve resolution-alternating least squares.

*N-PLS/RBL*: multidimensional partial least-squares/ residual bilinearization.

*PARAFAC*: parallel factor analysis.

*PMT*: photomultiplier tube.

*R*: correlation coefficient.

*SPE*: solid-phase extraction.

*SVD*: singular value decomposition.

*U-PLS/RBL*: unfolded partial least-squares/residual bilinearization.