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Comparison of different removal techniques for selected pharmaceuticals

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ABSTRACT

Recently, there is an emergence of endocrine-disrupting compounds, pharmaceuticals, and personal care products (EDC/PPCPs) as important pollutants to remove from drinking water and reclaimed wastewater. In this work, the efficiency of removing pharmaceuticals (PCs) from model aqueous solutions and raw wastewater with ultrafiltration (UF), nanofiltration (NF), activated carbon adsorption (AC), biological methods (SBR) and oxidation with ClO_2 was investigated. Some treatments have also been used as combined processes: UF+NF, UF+AC, SBR+ClO_2. Ibuprofen, Acetaminophen, Diclofenac, Sulfamethoxazole, Clonazepam and Diazepam were selected as model compounds. In order to evaluate their removal, PC solutions were also considered at several operating conditions (pH, conductivity, concentration, temperature), and optimal conditions were obtained. Experiments were performed at usual PC concentrations in wastewaters: 1000 ng/L for Ibuprofen and Acetaminophen, 300 ng/L for Diclofenac, Sulfamethoxazole, Clonazepam, and Diazepam. Separation was evaluated by liquid chromatography-mass spectroscopy. Results indicated that the removal efficiency depends on their Log K_{OW}, which is intrinsically related to

their hydrophobicity and then, to their adsorption onto the surface (UF, NF and AC). Also, NF, AC and combined processes (UF+NF, UF+AC) were the most suitable separation techniques to obtain high removal efficiencies for most of the PCs used, except for Acetaminophen (which showed great removal efficacy using SBR). UF presented low removal yields for all PCs tested. ClO_2 treatment was more effective at high concentration (50 mg ClO_2/L). Furthermore, results also showed that there are significant differences on the performance of the processes applied and which treatment is the most effective for each PC analyzed.

KEYWORDS: Pharmaceutical compounds, membrane processes, activated carbon, environmental analysis, hybrid process.

1. INTRODUCTION

The presence of pharmaceuticals and personal care products (PPCPs) in the environment is recognized as emerging issue due to their negative environmental and human health effects [1]. Pharmaceuticals (PCs) are introduced into the environment from discharges of wastewater treatment plants (WWTPs), which are not designed to treat all these substances and thus, they cannot be completely removed [2]. In this way, these effluents from WWTPs are relevant pollutant sources for the environment. Although PCs are present at very low concentrations (µg/L to ng/L range), they may cause environmental and health hazards [3]. Antimicrobial agents are the most widely used. As a major consequence, this usage could generate antibiotic-resistant bacteria, especially in quinolones and sulphonamides [4].

Furthermore, the application of sewage sludge to soils may be a potential route for these PCs to reach the terrestrial environment and then, the human food chain. In that way, it is not surprising that these antibiotics were detected even at subinhibitory concentrations in surface and groundwaters, treated wastewater, biosolids, soils, and sediments [5]. Removal efficiency for PCs at WWTPs depends on biological treatments [6], of which activated sludge process is the most

frequently used. Although some promising technologies have been implemented, more studies are required to develop really effective treatments, especially for the most persistent chemicals.

A combination between membrane filtration processes and biological treatment replaces advantageously a secondary clarification and tertiary steps. Ultrafiltration (UF) is used in wastewater treatment and drinking water production to remove natural organic matter (NOM) and micropollutants, such as pesticides and PCs [7,8]. In addition, these previous studies investigated different separation mechanisms (size/steric exclusion, hydrophobic adsorption, and electrostatic repulsion, among others). Recently, other membrane processes have been evaluated to remove PCs from wastewater. Nanofiltration (NF) has been used to successfully remove low-molecular-weight organic compounds such as pesticides, endocrine disruptors, and various PCs during water treatment [8-10]. This removal can occur through multiple mechanisms. At the beginning of the filtration process, removal can be governed by the adsorption phenomenon of different contaminants with hydrophobic nature or strong hydrogen-bonding characteristics [11-14]. Examples of this kind of contaminants are 2-naphthol, estrone, and non-phenolic pesticides. In many cases, removal can also occur through steady-state rejection. This may be due to steric effects for uncharged solutes or the combination of steric and electrostatic effects for charged solutes. These rejection mechanisms can affect different water-quality parameters including pH, ionic strength, and organic content [15].

The removal of PCs by adsorption is one of the most promising techniques. Adsorption process using activated carbon (AC) is frequently applied for removing natural or synthetic organic compounds (OCs) in drinking water treatment [16]. This process has numerous advantages: applicability at very low concentrations of pollutants, ease of operation, suitable for batch and continuous processes, possibility of regeneration and reuse, and low capital cost [17]. AC is a useful adsorbent to remove PCs due to its high surface area, high degree of microporosity, and well-developed surface chemistry properties. AC surface is predominantly hydrophobic but may also

contain functional groups formed during the activation process. These groups mainly contain oxygen and hydrogen, but they may also contain chlorine, nitrogen, and sulphur. The nature of these functional groups depends on activation conditions, which contribute to the acidic/basic character of the adsorbent surface and thus, it has influence on specific interactions with adsorbed compounds [18]. It has been demonstrated that the presence of oxygen-containing functional groups on the surface and their concentration levels play an important role in adsorption capability and removal mechanism [19-21]. Other important AC properties are: pore size distribution [20,22], ash content [23], and pH of point of zero charge (pHPZC), as an indicator of AC surface chemistry [24]. AC can be produced from several carbonaceous materials, including wood, coal, lignin, and coconut shells [25]. Recent studies have reported excellent performance of low cost ACs for the removal of pharmaceutical compounds, which is an attractive and economic alternative for water treatment along with waste disposal and recycling [24]. AC can be commonly found in two different forms: powdered activated carbon (PAC) and granular activated carbon (GAC). Several authors demonstrated the efficiency of both ACs (PAC and GAC) in the removal of organic micropollutants from water [26,27]. Since PAC is dynamically added to the plant, it can be used seasonally to treat wastewater in which the risk of OCs traces could be great (e.g., low-flow events). The capability of PAC to remove OCs depends on the PAC dose and the contact time, as well as the target contaminant properties (e.g. water solubility, hydrophobicity, charge, polarizability, size, aromaticity and the presence of specific functional groups) [20,28]. GAC used in packed bed filters was also highly effective. However, more hydrophilic contaminants can break the GAC filter much more rapidly than strongly bound hydrophobic contaminants. Therefore, in both powdered and granular forms, AC demonstrates a great potential for removal OCs traces, although PAC dose and GAC regeneration/replacement are two critical parameters to be considered for obtaining a successful removal [28]. Generally, loaded GAC is regenerated ex situ by heating [29] or steaming [30]. After several regenerations, GAC is managed as a waste and is incinerated [31].

Other interesting technique to remove PCs is using a Sequencing Batch Reactor (SBR), which is based on the principles of the activated sludge process. In a SBR, oxygen is bubbled through the wastewater to reduce biochemical oxygen demand (BOD) and chemical oxygen demand (COD). After that, the effluent is suitable to be discharged to surface waters or to be used in agriculture. The operation cycle is divided into five phases: filling, aeration-reaction, settling, decantation and idle. SBR has been successfully employed in the treatment of both municipal and industrial wastewater [32]. Moreover, it has been demonstrated that SBR is valid as a system to remediate polycyclic aromatic hydrocarbons (PAH) contaminated sediments, while offering a high flexibility to adapt the process to the characteristics of the compounds to be treated. For instance, if the value of the volumetric exchange ratio could be properly controlled, it would be possible to limit the pollutant load of the biomass in the SBR. So, it could be avoided the inhibition phenomena [33].

Additional chemical oxidation step can be used in WWTPs if the pollutants are not completely removal by biological treatment [34,35]. Among the chemical oxidants used in wastewater treatment, chlorine dioxide (ClO_2) is an interesting compound due to its potential to remove PCs in wastewater. The application of ClO_2 to remove PCs from drinking water, surface water and wastewater effluents has shown promising results. The non-steroidal anti-inflammatory drug Diclofenac, reported as one of the most frequently detected compounds in water at concentrations up to the mg/L level [36], is completely degraded during water treatment with low ClO_2 doses [37]. In wastewater effluents, steroid estrogens and industrial estrogenic chemicals were removed by using ClO_2 doses between 1.25 and 3.75 mg/L. At the same time, the reduction of estrogenic potency was observed [38]. The capability of ClO_2 as an oxidant has also demonstrated in the removal of several antibiotics found in water effluents [39,40]. When ClO_2 was used in biologically treated wastewater for selective oxidation of organic micropollutants, it was found that smaller doses were rapidly consumed through reactions with soluble components in water. This fast consumption in wastewater was observed in previous studies by other authors [34,38,41]. Based on

134 ClO_2 reactivity in wastewater effluents, it has been suggested that ClO_2 could be used as an
135 alternative to ozone for the removal of micropollutants [42,43].
136
137 Taking into account all the information above mentioned, the aim of this work consists of
138 evaluating the removal efficiency of some common PCs (Ibuprofen, Acetaminophen, Diclofenac,
139 Diazepam, Clonazepam, and Sulfamethoxazole) from both model aqueous solutions and raw
140 wastewaters. As a novelty, the performance of the most often used techniques for removal PCs (UF,
141 NF, AC, SBR, and ClO_2) were compared to the efficiency achieved by combining these techniques
142 (AC+UF, UF+NF, SBR+ClO_2). In addition, best techniques to remove each PC in terms of removal
143 efficiency were suggested.
144
145 ## 2. MATERIALS AND METHODS
146 ### *2.1. Pharmaceutical Compounds*
147 The choice of pharmaceutical compounds and their respective concentrations were performed
148 according to their occurrence in the environment as explained above. The active principles and the
149 main characteristics of the target PCs extracted from literature [8,28,44-46] can be observed in
150 Table 1.
151
152 The compounds selected were studied at the same concentration to simulate raw wastewater that
153 was 1000 ng/L for Ibuprofen (Tarbis, Tarbis Farma, Spain) and Acetaminophen (Pensa, Pensa
154 Pharma, Spain), and 300 ng/L for Diclofenac (Voltaren, Novartis Farmacéutica, Spain),
155 Sulfamethoxazole (Septrin, UCB-Iberia, Spain), Clonazepam (Rivotril, Roche Farma, Spain) and
156 Diazepam (Prodes, Kern Pharma, Spain).
157
158 The pure active principles were obtained using the drugs from commercially available pad. The
159 proportionality factor between the weight of the pad and the amount of active principle contained in
160 it was calculated. PCs quantities are presented in Table 2. The effect of the remaining quantities of

161 excipients (mainly cornstarch in small amounts) did not significantly influence on the experimental
162 results [47].
163
164 *2.2. Membrane Processes*
165 2.2.1. Ultrafiltration
166 The first phase of the ultrafiltration experiment was focused on the determination of the
167 permeability coefficient. The membrane used is an IRIS one (Orelis, France), made of
168 polyethersulfone (PES), with a molecular weight cut-off (MWCO) of 3 kDa and an effective area of
169 90.28 cm^2. This membrane has similar MWCO range that those used for treating PCs by other
170 researchers [8]. Characterization experiment of UF membrane involves the determination of the
171 coefficient of permeability with deionized water at different transmembrane pressures (from 0.5 to 4
172 bar). After the experiments, this coefficient had a value of 55 $L/m^2 \cdot h \cdot bar$.
173
174 Experiments were carried out with two different simulate wastewaters. Wastewater Type I consisted
175 of different solutions of each pharmaceutical compound in deionized water, whereas wastewater
176 Type II is similar to Type I but adding bovine serum albumin (BSA) in its composition. According
177 to Liang *et al.*, this second model wastewater simulates a real wastewater from WWTP [48]. UF
178 experimental set up was described previously in detail in a previous paper [49]. Permeate flux and
179 rejection index were determined under the following operating conditions: temperature of 20 ºC,
180 feed flow rate of 50 L/h (cross-flow velocity of 0.3 m/s) and transmembrane pressure (TMP) of 1.5
181 bar. Flux and rejection measurements were performed after 1 hour (steady state conditions).
182
183 Rejection index was calculated according to the following equation (Eq. (1)):

184 $$E(\%) = \left(1 - \frac{C_{out}}{C_{in}}\right) \cdot 100 \qquad \text{Eq. (1)}$$

185 where C_{in} was the concentration upstream of the treatment and C_{out} was the concentration
186 downstream of the treatment.

187

188 2.2.2 Nanofiltration

189 NF tests were performed in a pilot plant with a spiral wound composite polyamide membrane
190 "Hydranautics ESNA1-LF2-2540" (Nitto-Denko, Switzerland). The experimental setup where these
191 tests were carried out was adapted to NF and was described elsewhere [50]. The characterization of
192 this NF membrane with deionized water showed a permeability coefficient of 4 $L/m^2 \cdot h \cdot bar$.

193

194 NF experiments were carried out at a temperature of 16.5 ºC, feed flow rate of 370 L/h and a TPM
195 of 15 bar, with a Type I feed. In addition, pH was modified in order to study its effect on the
196 removal efficiencies. Permeate flux and rejection index of each compound were determined after 30
197 minutes of filtration time. In a second stage, wastewater from a secondary treatment of a municipal
198 wastewater treatment plant (MWWTP) with pharmaceutical compounds (Type III) was used as a
199 feed solution.

200

201 After each membrane separation procedure (both UF and NF), membranes were cleaned using
202 chemical processes (alkaline solutions at pH = 10 and citric acid at pH = 3) and deionized water. In
203 this way, membrane permeabilities were re-evaluated in order to restore the initial values of
204 permeability. Also, both UF and NF experiments were repeated three times and the average was
205 used to evaluate the performance of these membrane processes.

206

207 *2.3. Activated Carbon*

208 Activated carbon was evaluated for removal of target PCs in wastewater Type II. Two
209 commercially available AC were evaluated: Clarimex 061 CAE and Epibon YM 12X40, both
210 provided by Chiemivall, Spain. Experiments were performed in a Jar test (Selecta) and the average
211 of three samples obtained for each test was used to evaluate the process performance. The doses and
212 contact times were based on full-scale treatment plants that frequently use AC. Therefore, a contact

213 time of 4 h followed by 60 h of settling and AC doses of 10 and 50 mg/L were evaluated.
214 Supernatant was collected and filtered to remove residual AC.
215
216 *2.4. Oxidation with chlorine dioxide*
217 Chlorine dioxide solutions with a concentration of 3000 mg/L were prepared by sequentially mixing
218 TwinOxide® reagents A (sodium chlorite) and B (sodium bisulphate) as it was indicated by the
219 manufacturer (Brenntag Iberia, Spain). To study the PCs oxidation, different chloride dioxide
220 concentrations (from 0 to 20 mg/L) from these solutions were mixed with samples of 400 mL of
221 each PCs solution (Type I). The mixed solutions were allowed to react in the dark for 17 h at
222 controlled temperature (22 ºC). After the reaction was complete, three samples of 250 ml of were
223 taken from each reaction to be analyzed.
224
225 *2.5. Sequencing Batch Reactor*
226 These experiments were performed in a SBR with a total volume of 10 L.. The reaction volume
227 used was 6 L. It was equipped with an air pump and an air diffuser to keep dissolved oxygen (DO)
228 above 3 mg/L, and a stirrer for mixing. Feeding and decanting were performed using two peristaltic
229 pumps. Reactor feed was a solution prepared with 4.5 g of peptone (Cultimed, Panreac Spain), 4.5 g
230 of meat extract (Cultimed, Panreac Spain) and 0.6 g of phosphor dissolved in tap water (Type IV).
231 The cycle period was divided into five phases: filling (0.5 h), aeration-reaction (6 h), settling (1 h),
232 decanting (0.25 h) and idle (0.25 h). The hydraulic retention time (HRT) for SBR experiments was
233 16 h. The cycle was repeated 18 times to allow cell acclimation and/or to obtain repetitive results.
234 Daily analysis of pH (Crison GLP 21+), conductivity (Crison GLP 31+), turbidity (Dinko
235 turbidimeter d-112) and COD (kits from Merck Spain) of the supernatant were carried out. The
236 effect of the ClO_2 solutions during the SBR experiments was also tested as a combined process to
237 be compared with SBR results. Concentration of mixed liquor suspended solids (MLSS) and mixed
238 liquor volatile suspended solids (MLVSS) were measured throughout the operation according to
239 standard methods [51].

The initial MLSS concentration was 2.5 g/L. After one week of feeding only with the above described simulated wastewater, pharmaceutical compounds were added to the feed solution once biomass was acclimated to the simulated wastewater.

2.6. Analytical method for PCs analysis

2.6.1. SPE for extraction of water samples

The process SPE/clean-up used for water samples was based on that reported by Petrovic *et al.* [52]. PCs were isolated from water samples (250 ml, pH neutral) using an Oasis HLB cartridge [poly (divinylbenzene-co-N-pyrrolidone)] preconditioned with 5 mL of methanol and 5 mL of Milli-Q water. Samples were passed through the cartridges at a flow rate of 10 ml/min and then cartridges were rinsed with 5 ml of Milli-Q water and dried under vacuum for 15 minutes. The analytes retained were eluted with 6 ml of methanol. The extract was evaporated under a gentle stream of nitrogen and reconstituted with 1 ml methanol/water (25:75, v/v), filtered using syringe poly (tetrafluoroethylene) (PTFE) filters (0.22 μm, Analisis Vinicos, Tomelloso, Spain) and injected into the HPLC-MS/MS for analysis.

2.6.2. LC-ESI-MS/MS

An 1260 Infinity Ultra High-Performance Liquid Chromatograph (UHPLC) tandem with a 6410 Triple Quad Mass Spectrophotometer (MS/MS) is used for separating and determining, both of them of Agilent Technologies (Santa Clara, CA, USA). The analytical column was Kinetex 1.7 μm XB-C18 (60 x 2.10 mm) from Phenomenex (Paris, France). PCs were determined in both positive and negative ionization modes. In positive ionization (PI), the mobile phase was eluent A (formic acid 0.1 % in methanol) and eluent B (formic acid 0.1 % in water) in a gradient programme that started at 20 % A for 0.1 min, increased linearly to 90 % A in 15 min, then increased to 98 % A in 15 min, hold for 8 min, and returned to the initial conditions after 1 min followed by 11 min of equilibration time. Flow rate used in these measurements was 0.2 mL/min. In negative ionization

(NI), the mobile phase was methanol with 5 mM ammonium formate as eluent A and ammonium formate 5 mM in water as eluent B, at a flow rate of 0.2 mL/min. A gradient programme was used as follows: 15 % of eluent A for 0.1 min, followed by a linear increase to 98 % in 5 min, held for 7 min. The injection volume was 20 µL. Compounds optimization was carried out with Optimizer program by Agilent Technologies. This program looks for the best transitions and conditions (the selected ones are shown in Table 3). Optimizer was configured to search a fragmentor from 5 to 200 V and this can search each 10 steps. Collision energy Optimizer should search from 10 to 150 V. NI searches preferably $[M-H]^-$ whereas PI mode $[M+H]^+$,$[M+NH_4]^+$ and $[M+Na]^+$ [53].

2.6.3. Validation of the analytical method

Linearity was studied using standard solutions and matrix matched calibrations by analysing in triplicate seven concentration levels, between 7.5 and 7500 ng/mL in the final extract, equivalent to 0.030 and 30 µg/L. Matrix effects were studied by comparison of the slopes of both regression equations. Samples were spiked with the analytes at 0.5 µg/L for water under the conditions described above. The limit of detection (LOD) and the limit of quantification (LOQ) were calculated as the amount of the analyte with a signal-to-noise ratio (SN) of 3 and 10, respectively [54]. Method LODs are outlined in Table 4.

3. RESULTS AND DISCUSSION

3.1. Results of UF process

Table 5 shows the PCs rejection obtained during the UF tests carried out with two different simulated wastewaters (Types I and II). The value of each parameter listed in this table is an average of that obtained in three independent experiments. Results indicated low rejection values for all PCs tested using Type I feed wastewater, which are similar to those obtained by Acero *et al.* in UF experiments with a PES membrane of 5000 Da [55]. However, three PCs (Ibuprofen, Diclofenac and Diazepam) presented higher rejection values during UF than the other compounds tested. The behaviour showed by these PCs could be intimately related to their Log K_{OW} (logarithm

294 of the octanol-water partition coefficient), which indicates the hydrophobicity of an organic
295 compound and it is often used to describe the sorption potential of PCs in the aquatic environment
296 [56]. The PCs with high retention value during UF process have a Log K_{OW} next to 3 (Diazepam) or
297 even higher (Ibuprofen and Diclofenac), where these results are in accordance with those obtained
298 by other researchers. Lopez-Fernandez *et al.* [57] demonstrated that the PC adsorption on the
299 membrane surface (in their case, PVDF membrane) is related to the Log K_{OW} value. When this
300 value is low (< 2.6), PCs have low lipophilicity and high hydrophilicity which indicates that these
301 PCs are not adsorbed on the membrane surface (generally unmodified PVDF and PES have
302 hydrophobic character [58,59]). On the other hand, when PCs have high Log K_{OW} (> 4.5), the
303 opposite effect is observed, being these compounds adsorbed on membrane surfaces [57]. Also,
304 Yoon *et al.* demonstrated for UF and NF experiments that PCs with high average retention
305 percentage had a Log K_{OW} value higher than 3, which indicates that retention for hydrophobic
306 membranes is influenced by hydrophobic interaction (adsorption) [8]. So, based on the results
307 obtained by these researchers, the PCs could be adsorbed on the membrane surface depending on
308 their Log K_{OW} value. Diclofenac presented the highest rejection value and then, the highest
309 adsorption on the surface of the PES membrane used because this molecule has the highest Log
310 K_{OW} value among all the PCs tested.
311
312 When Type II wastewater was used as feed solution (with BSA in its composition), slightly higher
313 rejection values were obtained for Diazepam. However, a huge increase in rejection values was
314 observed for Ibuprofen, Sulfamethoxazole and Diclofenac, where the latter presented the highest
315 rejection values among all the PCs tested (42.2 %). Chon *et al.* performed similar UF experiments
316 with Diclofenac and Sulfamethoxazole, obtaining similar rejection values [45]. The increase in PCs
317 rejection values using wastewater Type II could be due to their adsorption onto the proteins, which
318 may form aggregates with higher size than the dissolved protein in the solution [60]. Other
319 researchers as Sharma *et al.* studied the BSA interaction with two different PCs (Diclofenac sodium
320 and Cefotaxime sodium) and they observed that the binding affinity of both PCs with BSA was

high in a range of temperatures between 10 and 35 ºC. They also demonstrated that a tighter binding BSA and Diclofenac occurred [61]. In addition, Karpii *et al.* corroborated that the presence of albumin in serum diminished the adsorption of PCs onto a PVDF modified membrane [46].

3.2. Results of NF process

NF reached high PCs removal efficiencies (between 60 and 92 %) with the exception of Acetaminophen (~2 %) as it is shown in Table 5. These results for this compound could be due to its low Log K_{OW} value (0.46), as it was explained in section 3.1, its low molecular weight (151.2 g/mol) and its neutral charge [57]. The difference between the Acetaminophen removal and the other PCs was higher in NF because the electrostatic repulsion forces between the membrane (polyamide) and the PC exerted more influence on membrane separation than in UF processes during the removal of the rest of PCs. Unlike some results reported by other authors [55], PCs removal efficiencies obtained in this work are slightly higher, due to the low MWCO of the membrane used (between 70 and 80 % of sodium chloride rejection under standard solutions according to the membrane supplier).

The influence of pH solution on the PCs removal was considerable, especially in the case of Clonazepam, because the reduction of pH from 8.5 to 6.5 led to an increase in its removal efficiency from 22 to 80 % (see Table 5). Other researchers studied the pH influence on the rejection of PCs as one of the most important parameters that could affect the performance of UF, NF and RO membranes [45], Among all the PCs studied, the removal of Clonazepam is heavily influenced by changing the pH of the aquatic environment. The results for this compound reveal that the removal efficiency slightly decreased between pH values of 6.11 (80.33 %) and 6.48 (74.54 %). However, this removal efficiency vastly declined to 24.81 % at a pH value of 8.5. According to the pKa values for Clonazepam (1.5 y 10.5) presented in Table 1, this compound is protonated at highly acidic conditions and it becomes non-protonated (neutral) when pH values increases up to 6, as was demonstrated in separated studies by Miri and Jalali[62] and García and Perillo[63]. But, at alkaline

conditions, the compound changes to its enolic form, which has enhanced its affinity to water due to the presence of charge on the molecule [62, 63]. This increase in water affinity leads to a lower retention of the PC molecule onto the membrane surface and therefore, its removal efficiency decreases.

Results of the tests performed with Type II wastewater and with secondary effluent plus PCs (Type III) are also presented in Table 5. It can be observed that NF was still slightly more effective than in the case of Type I water (80-90 % of retention indexes). This behaviour could be explained by the interaction between PCs and organic compounds remaining in the secondary effluent, mainly proteins and carbohydrates coming from the release of cellular material. Acetaminophen was also the PC with the minimum rejection, though values were considerable higher than in the tests with synthetic solutions (55.34 %).

3.3. Results of the activated carbon tests

In this section, results of the experiments with activated carbon using the source water Type II, with and without previous UF, are reported.

3.3.1. Activated Carbon

Table 6 shows the removal efficiency for all PCs using AC. Great removal efficiencies were obtained for both ACs, especially at high AC concentration (50 mg/L). Thus, the increase of the concentration of both activated carbons coincided with an increase in their removal efficiency, with the only exception of Diclofenac (82.7 % → 70.2 %) in the case of the use of Epibon (pulverized granular activated carbon). This result could be associated with the hydrophobic character of Diclofenac (high Log K_{OW}) and the competitive inhibition of BSA with Diclofenac onto the activated carbon [64]. Only Acetaminophen had poor removal efficiency with Epibon 10 mg/L (only 12.9 %). According to Delgado *et al.*, Log K_{OW} could be a reasonable indicator of PCs removal when adsorption was only caused by hydrophobic interactions [65]. However, it cannot be

considered an appropriate indicator for the adsorption of several compounds, for example for whose that contain heterocyclic or aromatic nitrogen, where electrostatic interactions, chemical bounding and non specific forces between the adsorptive and the AC surface are omitted through an exclusive Log K_{OW} approach.. In addition, the removal efficiency was mostly dependent on the volume of the largest micropores of AC, because the solvation effect may enlarge the solute molecular dimensions thus hindering its access and packing in the narrower micropores. Moreover, Ji *et al.* observed that the adsorption of many antibiotics probably referred to a prominent size-exclusion effect when these compounds were adsorbed onto microporous ACs, because the porous structure of commercial ACs principally consisted of micropores with irregular-shaped and modestly closed pore structures [16].

3.3.2. Activated Carbon/Ultrafiltration combined process

AC-UF system, which combines AC adsorption with low-pressure driven membrane filtration, showed great potential to adsorb pharmaceutical compounds (80-95 %), as it is displayed in Table 6. All views expressed previously on activated carbon remain valid, showing this technique high efficiency in all the samples analysed. It was also observed that a combined process AC+UF improves the results obtained with AC treatments, especially at low AC concentrations. For Acetaminophen, these two technologies combined in series had low removal efficiency (~28-44 % with 10 mg/L and ~53-58 % with 50 mg/L) as already seen from the results separately obtained for UF and AC tests.

3.4. Chlorine dioxide results

Among the six investigated compounds, only Diazepam showed an appreciable reactivity, as it is seen in Figure 1. Results obtained for Diazepam showed that an increase in ClO_2 concentration coincided with an increase in the removal efficiency, achieving values of 66 %. Therefore, it could be concluded that ClO_2 applied in water treatment only acted as a partial barrier for PCs, even though it is relatively effective in oxidizing antibiotics and estrogens. These two compounds merit

special concern due to their high biological activity. This is in accordance with the results reported by Huber *et al.*, even though results are not fully comparable, because they investigated three different water sources (drinking water, lake water, groundwater) and used different experimental conditions: lower ClO_2 concentrations, variable time reaction, and higher compounds concentration (~µg) [37]. However, they obtained good removal values for Sulfamethoxazole and Diclofenac, justifying according to the reactivity of the aniline group (contained in both compounds) to ClO_2 and because the deprotonation of acidic nitrogen of the sulfonamide moiety enhanced the reactivity of Sulfamethoxazole. Hey *et al.* investigated several compounds, but they do not study Diazepam and they also used higher concentrations (100 mg). The poor efficiency of this treatment could be due to the lower concentration used and the dependence of the degree of oxidation on the type of wastewater. Furthermore, reactivity of the compounds depended on the reactive functional group present [66].

3.5. SBR results

This type of treatment had different results depending on the pharmaceutical component analysed. SBR results without and with ClO_2 in terms of removal efficiency were presented in Table 7. Good results for Ibuprofen and Acetaminophen (~90-95 % for both compounds) were observed, whereas scarce removal efficiencies were shown for Diclofenac (~25 %), Sulfamethoxazole (~20 %), and Diazepam (~15 %). Regarding the Clonazepam, removal efficiency presented very acceptable results (~85 %). During the operation time of all of these processes, MLSS, MLVSS, pH, conductivity, turbidity and COD were also measured and their results are shown in Table 8. Before the addition of ClO_2, the different parameters measured during SBR tests did not change significantly. After the addition of ClO_2 to SBR, an initial decrease in biomass parameters as well as an increase in conductivity was detected. In the same way, the presence of ClO_2 led to a general increase in the removal efficiency in the first days of treatment. There are no similar data present in literature, in fact Elmolla and Chaudhuri investigated different PCs (Amoxicillin and Cloxacillin), at different working conditions (1.5 L in volume and a biomass concentration of 2300 mg/L) and

with Fenton pre-treatment system. They defined the best operating conditions for treatment of the antibiotic wastewater by combined Fenton-SBR process, which were H_2O_2/COD molar ratio 2.5, H_2O_2/Fe^{2+} molar ratio 150, Fenton reaction time 120 min and a HRT of 12 h. Under these conditions, they obtained a removal efficiency of 89 % for COD removal and the SBR effluent met the discharge standards [67].

3.6. Results for single compound

This section has the aim of summarizing all the results obtained for each PC studied, which are displayed in Tables 5-7. In this way, it will be clear which processes may be the most effective for their separation.

Ibuprofen had very poor percentages of removal with UF treatments (36.33 %), but excellent removals when UF is combined with NF (≥ 99 %). These results are higher than those obtained using only NF (75-90 %). Excellent results were also obtained with AC treatments at high AC concentration (≥ 95 %), and with SBR during the first days of the cycle (≥ 95 %).

Acetaminophen had generally low removal efficiencies using NF experiments at different pHs (≤ 13 %). These results could be attributed to its low molecular weight and its low value of Log K_{OW} (values displayed in Table 1), as it was explained in sections 3.1 and 3.2. UF processes were also ineffective (~1.6 %), in contrast to SBR results, which presented high percentages of removal (≤ 95 %).

For Diclofenac, AC+UF had excellent removal efficiencies (≥ 95 %), which were better than those obtained when both processes were individually implemented (≥ 68 % for AC and 42.2 % for UF). The same trend is observed for the combination of UF+NF, which gave excellent results (≥ 98 %). SBR processes (with and without ClO_2) had very low removal efficiencies (~10-38 %).

456 The AC treatments applied for removal Sulfamethoxazole had good removal efficiencies, especially
457 excellent results were obtained at high AC concentrations (≥92 %). These results improved when
458 AC was combined with a UF process (~96-99 % with 50 mg/L). UF treatments had poor efficiency
459 (~10-21 %), while NF processes presented excellent results (~70-98 %). Regarding the results for
460 SBR processes (with and without ClO_2), very low removal efficiencies (~19-40 %) were obtained.
461
462 For the benzodiazepines studied, Clonazepam had excellent removal efficiencies during NF
463 treatment of real wastewater (≥ 90 %) and at pH next to 6 (≥ 74 %), but these values decreased to
464 25 % at pH = 8.5 when this compound changed to a enolic form (as it was indicated in section 3.2).
465 Regarding the SBR results, they suggested an increase in the efficiency of removal during the
466 course of the days (~70-85 %), but in the case of introduction of ClO_2 the long-term interaction with
467 the biomass decreased and consequently the effectiveness of removal (41.5 %). In the case of
468 Diazepam, it had excellent removal percentages when was treated using NF process (≥ 88 %), AC
469 treatment at low concentrations (≥ 93 %), but poor efficiencies with UF (~19 %). Among all the
470 PCs tested, this compound is the only one that showed an increase in the removal efficiency using
471 ClO_2, which increased when ClO_2 concentration was higher. Finally, poor results were obtained
472 with SBR processes (~15 % without ClO_2 and ~39 % with ClO_2).
473
474 **4. CONCLUSIONS**
475 The removal efficiency of six different pharmaceuticals using several separation techniques was
476 studied to determine the most appropriate method for each pharmaceutical. In the case of membrane
477 processes, UF was practically ineffective for all the compounds tested, obtaining the best removal
478 efficiencies for all compounds using NF process, except for Acetaminophen and Ibuprofen. Both
479 compounds presented the highest removal percentages with SBR, but this treatment had lower
480 removal efficiencies for the remaining pharmaceuticals, for which NF process was better. As
481 regards the AC tests, these experiments had excellent removal efficiency for almost all the
482 pharmaceuticals examined (especially at high AC concentration, 50 mg/L), except for

483 Acetaminophen. Therefore, Acetaminophen is the pharmaceutical compound with most difficulties
484 to be treated, due to the low effect of the treatments used along this study. In addition, Diazepam is
485 the only compound that showed an increase of the removal efficiency with ClO_2. Also, an increase
486 in ClO_2 concentration gradually led to a better removal results. Finally, the combined UF+NF
487 process was the most effective of all the treatments performed.
488
489 For all pharmaceuticals, a general trend appeared with higher mass recovery at high Log K_{OW}.
490 Although experimental and analytical accuracy could vary the mass recovery, these results
491 indicated that observed retention for the relatively hydrophobic compounds based on their Log K_{OW}
492 was significantly governed by adsorption.
493

494 ## 5. ACKNOWLEDGEMENTS

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497

498 ## 6. REFERENCES

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Table 1. Main characteristics of the selected pharmaceuticals used in this study.

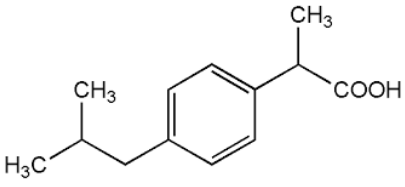
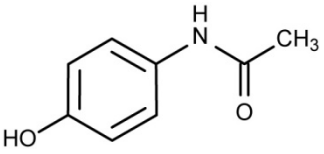
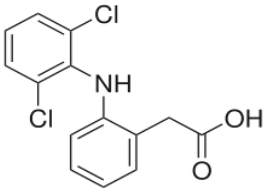
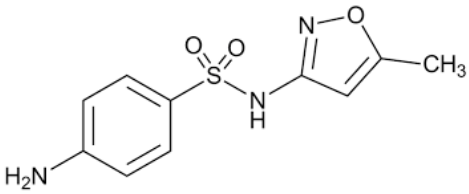
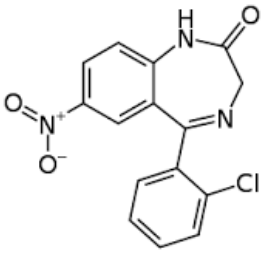
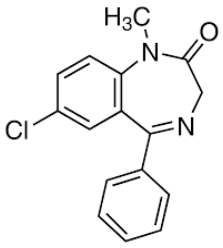
Pharmaceutical compound	Structure	Molecular weight (g/mol)	Log K_{ow}	pK_a	Ref.
Ibuprofen		206.29	3.97	4.91	[44]
Acetaminophen		151.2	0.46	9.4	[8]
Diclofenac		296.14	4.51	4.15	[45]
Sulfamethoxazole		253.28	0.89	5.5	[28]
Clonazepam		315.71	2.41	10.5 (1-position) 1.5 (4-position)	[46]
Diazepam		284.80	2.82	3.3	[8]

Table 2. Active principle and quantities of the pharmaceuticals used.

Pharmaceutical names	Active principle	Weight a single pad (mg)	Weight active principle for pad (mg)	Proportional parameter
Tarbis	Ibuprofen	771.3	600	1.2855
Acetaminophen Pensa	Acetaminophen	1308.4	1000	1.3084
Voltaren	Diclofenac	210.9	50	4.218
Septrin	Sulfamethoxazole	501.6	400	1.254
Rivotril	Clonazepam	153.8	0.5	307.6
Diazepan Prodes	Diazapem	77.7	2.5	31.08

Table 3. Experimental parameters of the analytical method used.

Compound	Frag (V)	Quantification transition	CE (V)	Frag (V)	Confirmation transition	CE (V)
PI Mode						
Diazepam	156	285 →193	34	156	285 →154	26
Clonazepam	136	316 →270	24	136	316→214	35
Acetaminophen	112	152 → 110	13	112	152 → 65	33
Sulfamethoxazole	104	254 → 156	10	104	254 → 92	26
NI Mode						
Ibuprofen	68	205 → 161	2		-	-
Diclofenac	88	294 → 249	10	88	294 → 178	22

Table 4. Limit of detection values (LOD) for all the compounds tested.

Compound	LOD
Ibuprofen	6.8 ng/L
Diazepam	0.3 ng/L
Clonazepam	0.5 ng/L
Acetaminophen	0,9 ng/L
Diclofenac	2,5 ng/L
Sulfamethoxazole	0,9 ng/L

Table 5. Removal efficiencies (%) for each selected pharmaceutical compound using different membrane separation processes and wastewaters (Type I, II and III).

Pharmaceutical compound	UF		NF				UF + NF
	Type I	Type II	Type I (pH=6.11)	Type I (pH=6.48)	Type I (pH=8.5)	Type III	Type II
Ibuprofen	12.21	26.33	80.51	86.57	91.38	87.18	95.18
Diazepam	18.98	19.14	87.41	90.96	91.28	91.37	99.69
Acetaminophen	Non detected	1.60	1.62	4.91	12.60	55.34	76.50
Sulfamethoxazole	10.70	20.80	---	70.78	---	98.21	99.90
Clonazepam	---	---	80.33	74.54	24.81	90.32	---
Diclofenac	24.70	42.20	66.91	68.69	76.45	82.99	98.14

Table 6. Removal efficiencies (%) for each selected pharmaceutical compound using two different activated carbons (Clarimex and Epibon) and a combined hybrid process (activated carbon and ultrafiltration).

Pharmaceutical compound	AC				AC + UF			
	Clarimex (10 mg/L)	Clarimex (50 mg/L)	Epibon (10 mg/L)	Epibon (50 mg/L)	Clarimex (10 mg/L)	Clarimex (50 mg/L)	Epibon (10 mg/L)	Epibon (50 mg/L)
Ibuprofen	43.02	99.00	77.20	95.35	63.72	99.90	85.48	97.04
Diazepam	94.59	97.04	93.66	97.02	95.63	97.61	94.88	97.60
Acetaminophen	32.10	43.00	12.90	48.60	44.00	53.00	28.20	57.60
Sulfamethoxazole	54.00	92.30	71.90	94.20	67.90	94.60	80.40	96.00
Diclofenac	68.00	99.00	82.70	70.20	95.80	99.90	97.80	96.10

Table 7. Removal efficiencies (%) for each selected pharmaceutical compound using SBR and SBR+ClO_2 processes.

Pharmaceutical compound	SBR		SBR + ClO_2		
	4th day	8th day	1st day	4th day	8th day
Ibuprofen	89.40	94.59	90.35	96.08	93.74
Diazepam	2.78	15.22	39.27	30.11	13.95
Acetaminophen	94.19	90.55	97.46	95.79	54.40
Sulfamethoxazole	19.21	20.33	29.91	40.54	25.64
Clonazepam	52.54	84.93	71.87	72.11	41.50
Diclofenac	10.29	25.93	10.58	37.56	25.96

Table 8. SBR experimental results.

Day of process	MLSS [mg/L]	MLVSS [mg/L]	volatile [%]	pH	Conductivity [µS/cm²]	Turbidity [NTU]	COD [mg/L]
1	1.175	0.993	84.511	-	-	-	-
2	1.098	0.960	87.432	7.30	1070	10.70	-
3	1.999	1.775	88.794	7.16	1035	-	-
4	2.311	2.009	86.932	7.05	1017	-	-
7 (pharma)	2.784	2.376	85.345	7.18	1032	2.02	16.90
8	2.876	2.558	88.943	7.18	1045	-	-
9	2.833	2.495	88.069	7.73	1064	-	-
10 (after purge)	2.408	2.208	91.694	7.12	1042	-	-
11	2.763	2.514	90.988	7.55	1062	-	-
14 (ClO_2)	2.758	2.562	92.893	7.57	1009	2.58	18
15	2.754	2.478	89.978	7.45	1053	-	-
16	2.539	2.277	89.681	7.70	1141	-	-
17	2.333	2.120	90.870	7.69	1133	-	-
18 (after purge)	2.518	2.258	89.674	7.60	1134	-	-
21	2.641	2.350	88.981	7.33	1068	3.95	20.05

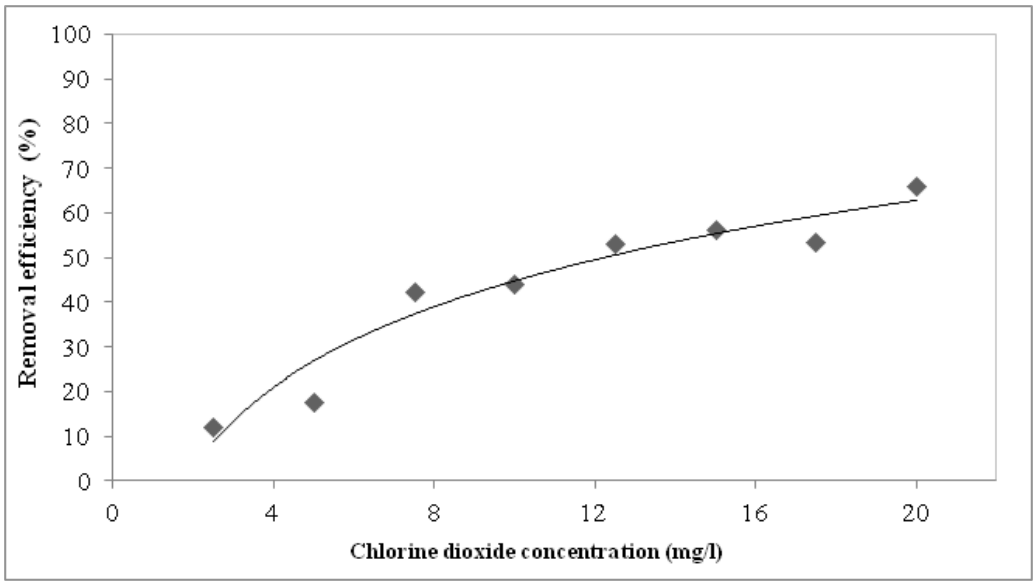


Figure 1. Removal efficiencies (%) of Diazepam at different ClO_2 concentrations.