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Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment

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ABSTRACT

This paper investigates the removal of a broad range of pharmaceuticals during nanofiltration (NF) and reverse osmosis (RO) applied in a full-scale drinking water treatment plant (DWTP) using groundwater. Pharmaceutical residues detected in groundwater used as feed water in all five sampling campaigns were analgesics and anti-inflammatory drugs such as ketoprofen, diclofenac, acetaminophen and propyphenazone, β-blockers sotalol and metoprolol, an antiepileptic drug carbamazepine, the antibiotic sulfamethoxazole, a lipid regulator gemfibrozil and a diuretic hydrochlorothiazide. The highest concentrations in groundwater were recorded for hydrochlorothiazide (58.6–2548 ng L^{-1}), ketoprofen (<MQL–314 ng L^{-1}), diclofenac (60.2–219.4 ng L^{-1}), propyphenazone (51.5–295.8 ng L^{-1}) and carbamazepine (8.7–166.5 ng L^{-1}). Excellent overall performance of both NF and RO was noted, with high rejection percentages for almost all of the pharmaceuticals investigated (>85%). Deteriorations in retentions on NF and RO membranes were observed for acetaminophen (44.8–73 %), gemfibrozil (50–70 %) and mefenamic acid (30–50%). Furthermore, since several pharmaceutical residues were detected in the brine stream of NF and RO processes at concentrations of several hundreds nanogram per litre, its disposal to a near-by river can represent a possible risk implication of this type of treatment.

1. Introduction

Demand and competition for scarce water resources is expected to increase in the coming decades. According to the predictions of Consultative Group on International Agricultural Research (CGIAR), 2.7 billion people will be living in water-scarce regions by the year 2025. Surface and groundwater are the major renewable resources for sustainable drinking water production throughout the world. However, research is documenting with increasing frequency that many chemical constituents that have not been considered historically as contaminants are present not only in wastewater, but also in natural waters at global scale (Kolpin et al., 2002; Ternes, 1998; Snyder et al., 2003; Halling-Sørensen et al., 1998). These "emerging contaminants" are commonly derived from municipal, agricultural and industrial wastewater sources and pathways due to often inadequate treatment in conventional wastewater treatment plants (WWTPs) (Ternes, 1998;

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Radjenović et al., 2007; Stumpf et al., 1999), thus they are detected in rivers downstream (Kolpin et al., 2002; Abuin et al., 2006; Ellis, 2006). Dilution that occurs between the point of discharge (i.e., WWTP) and downstream usage and/or groundwater wells may not be enough in some cases. For example, pharmaceutical residues clofibric acid, diclofenac and propyphenazone were detected in Berlin tap water at low ng per litre level (Heberer, 2002). If their elimination in DWTPs is not complete, they may reach the customer through drinking water at trace level concentrations (Heberer, 2002; Heberer and Stan, 1997; Reddersen et al., 2002; Frick et al., 2001), and have subtle effects on human health (Kümmerer, 2001). Persistence of pharmaceutical residues was demonstrated for common treatments applied in DWTPs, such as sand filtration (Ternes et al., 2002) chemical coagulation/flocculation (Vieno et al., 2006; Adams et al., 2002) and chlorination (Gibs et al., 2007). Ultraviolet (UV) radiation could be another option, but due to high UV doses required it will not be economically competitive with other types of treatment (Snyder et al., 2003). Advanced techniques such as ozonation, advanced oxidation processes (AOP) and activated carbon are considered to be more efficient in eliminating polar pharmaceuticals (Ternes et al., 2002). Also, techniques that have been gaining attention in the past few years are pressure-driven membrane processes nanofiltration (NF) and reverse osmosis (RO). These two treatments seem to be able to effectively remove most organic and inorganic compounds and microorganisms from raw water (Chellam et al., 1997; Gagliardo et al., 1998) and their application in drinking water treatment has been the focus of attention of many researchers.

As far as pharmaceuticals are concerned, several studies were published investigating mechanisms of their rejection on NF/RO membranes (Yoon et al., 2006; Kimura et al., 2003a; Kimura et al., 2003b; Kimura et al., 2004; Nghiem et al., 2005; Snyder et al., 2007; Košutic et al., 2007). However, these investigations were meagrely performed on a laboratory scale and in many cases with demineralised water. There are very few studies published on the performance of a full-scale NF/RO treatment in rejecting micropollutants such as endocrine disrupting compounds (EDCs) and pharmaceuticals (Snyder et al., 2007; Al-Rifai et al., 2007), mostly reporting their complete removal. However, in these studies NF and RO membranes were employed as tertiary treatment in wastewater recycling plant or for treating saline groundwater. Moreover, most studies primarily focus on the permeate concentrations of micropollutants, while concentrate characteristics are rarely monitored. In a previously published work by Nghiem and Schäfer (2006), importance of membrane cleaning solution treatment was emphasized, when dealing with water contaminated with EDCs.

In this study performances of full-scale NF and RO drinking water treatments in rejecting pharmaceutical residues were investigated. Out of the 31 compounds included in the analytical method, belonging to different therapeutic groups and having diverse physico-chemical properties, 12 were frequently detected in groundwater wells. Table 1 summarizes the structures and physico-chemical properties (i.e., pK_a and $\log K_{OW}$) of the encountered compounds. The results confirmed a very good performance of full-scale NF and RO in removing pharmaceutical residues contained in the exploited groundwater resource. Moreover, brine stream concentrations of pharmaceuticals rejected on the membranes in DWTP are also reported, whereas they were concentrated by a 3–5 fold factor over the raw water.

2. Experimental

2.1. Materials and standards

Chemical standards for carbamazepine, lansoprazole, loratidine, famotidine, trimethoprim, ofloxacin, atenolol, metoprolol, azithromycin dihydrate, erythromycin hydrate, fluoxetine hydrochloride, ranitidine hydrochloride, sulfamethoxazole, propranolol hydrochloride, indomethacin, acetaminophen, mefenamic acid, clofibric acid, bezafibrate, mevastatin and sotalol hydrochloride were purchased from Sigma–Aldrich (Steinheim, Germany). Propyphenazone, pravastatin and paroxetine hydrochloride were from LGC Promochem (London, UK). Ketoprofen, diclofenac, gemfibrozil, ibuprofen and naproxen were from Jescuder (Rubí, Spain). Glibenclamide was purchased from SIFA Chemicals (Liestal, Switzerland), and hydrochlorothiazide was supplied by PLIVA (Zagreb, Croatia). All pharmaceutical standards used were of high purity grade (>90%).

Isotopically labelled compounds used as internal standards were ^{13}C-Phenacetin obtained from Sigma–Aldrich, mecoprop-d_3 from Dr. Ehrenstorfer (Augsburg, Germany), ibuprofen-d_3, atenolol-d_7 and carbamazepine-d_{10} from CDN Isotopes (Quebec, Canada). All solvents (methanol, acetonitrile and water) were HPLC-grade and were purchased from Merck (Darmstadt, Germany), as well as hydrochloric acid (HCl, 37%), ammonium-acetate (NH_4Ac) and acetic acid (HAc). Nitrogen for drying 99.995% of purity was from Air Liquide (Spain).

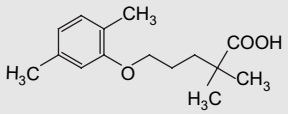
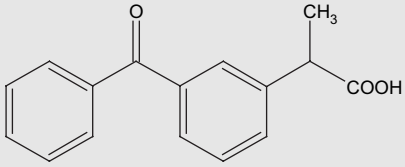
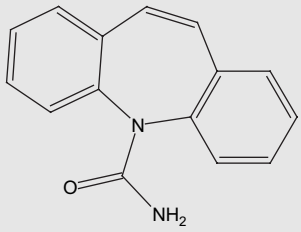
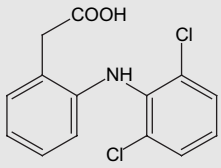
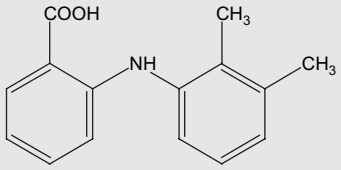
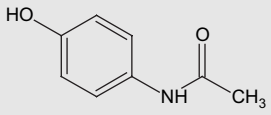
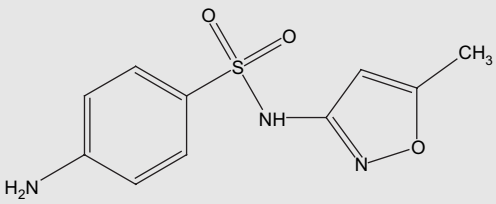
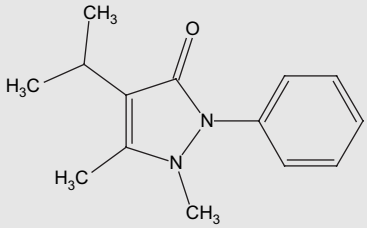
Stock solutions of individual standards (1 g L^{-1}) and internal standards were prepared in methanol and stored at −20 °C. Stock solutions of ofloxacin, pravastatin and sulfamethoxazole were renewed monthly before their use due to their limited stability (Gros et al., 2006). A standard mixture in which the compounds were at a concentration of approx. 20 mg L^{-1} was prepared from the stock solutions. Further dilutions of this mixture were prepared in methanol–water (25:75, v/v) and were used as working standard solutions. A mixture of internal standards prepared by dilution of individual stock solutions in methanol was used for an internal standard calibration.

2.2. Nanofiltration and reverse osmosis waterworks

The sampled DWTP located in NE-Spain is able to treat 720 $m^3 h^{-1}$ and supplies drinking water to around 50,000 inhabitants. The DWTP works with three treatment lines operating in parallel, one equipped with NF, and two lines equipped with RO membrane filtration racks (see Fig. 1). All three lines are fed from groundwater wells, directly influenced by infiltration from Besós River, a Mediterranean river with extremely irregular flow during the year (average annual flow is 4.3 $m^3 s^{-1}$).

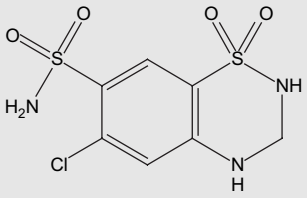
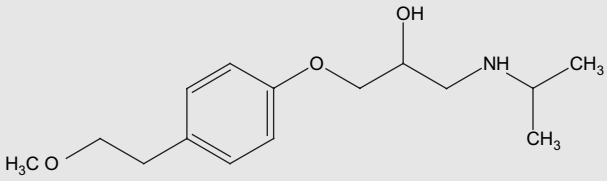
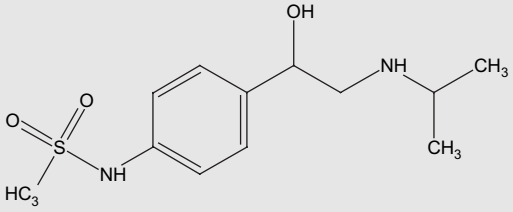
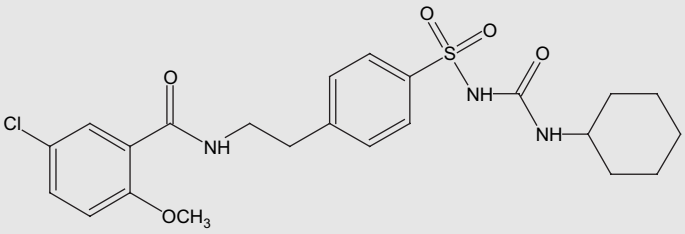
Each RO treatment line is designed for a feed flow of 486 $m^3 h^{-1}$, whereas maximum flow of NF line is 360 $m^3 h^{-1}$. Permeate flows of the two RO and NF lines are 356.4 $m^3 h^{-1}$

Table 1 – Selected pharmaceuticals, their structures and physico-chemical properties

Compound	Structure	MW (g mol^{-1})	pK_a[a]	log K_{OW}[b]
Gemfibrozil		250.33	4.43	4.77
Ketoprofen		254.28	4.45	3.12
Carbamazepine		236.27	13.9	2.45
Diclofenac		296.15	4.2[c]	4.6[d]
Mefenamic acid		241.28	4.2	5.12
Acetaminophen		151.16	9.38	0.46
Sulfamethoxazole		253.28	pK_1 5.7 pK_2 1.8	0.89
Propyphenazone		230.30	–	1.94

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	MW (g mol^{-1})	pK_a[a]	log K_{OW}[b]
Hydrochlorothiazide		297.74	7.9	−0.07
Metoprolol		267.36	9.6	1.88
Sotalol		272.37	pK_1 8.2 pK_2 9.8	0.24
Glibenclamide		494.01	−(6.3[e])	4.79

a pK_a values were retrieved from PhysProp Database Demo, Syracuse Research corporation, 2007 (http://www.syrres.com/esc/physdemo.htm).
b log K_{OW} values are for neutral molecule form; based upon Syracuse Research corporation, 2007; LOGKOW/KOWWIN Program (http://www.syrres.com/esc/est_kowdemo.htm).
c Jones et al. (2002).
d Hansch et al. (1995).
e Sheppard and Robinson (1997).

and 234 m^3 h^{-1}, thus affording permeate recoveries (i.e., conversions of feed water to permeate) of 73% and 65%, respectively. The RO rack consists of two parallel stages, whereas the first has 40 membrane modules and the second one 20 (each one consists of 6 RO membranes type BW30LE-440, Dow FilmTec). The NF line comprises also two stages, with 31 and 15 membrane modules, respectively, equipped with six NF membranes (NF90-400, Dow FilmTec) each. Membrane characteristics and operating conditions of NF and RO membranes are summarized in Table 2. The treatment consists of pre-treatment (UV radiation, filtration and conditioning), NF/RO filtration and post-treatment (remineralisation, pH correction, stripping by CO_2 and post-chlorination). The pH of entering groundwater was around pH 7.4, whereas operating pH of NF and RO stages was in the range pH 5.6–6.1. The temperature of water was around 17 °C.

In the pre-treatment, filtration of entering groundwater is achieved by two cartridge filters (selectivity 1 μm; each filter has 180 cartridges) which are functioning alterably: when the filter in operation gets abrupt by impurities, the other one is set to function while the first one is being cleaned. Before and after the cartridge filters, water is conditioned with sodium bisulphite that prevents bacterial growth, reduces water oxygen content (that causes corrosion), and lowers its pH. Moreover, a dispersant is added in order to lower water hardness. During the pre-treatment, UV radiation is used to sterilize the entering water before its entrance to the membrane's rack. The UV lamps used for disinfection stage are low pressure mercury lamps (LP Hg lamps), whereas the UV dose applied is 400 J m^{-2}. After the membrane filtration stage, treated water from all three lines is being further processed before sending to distribution system in a joint post-

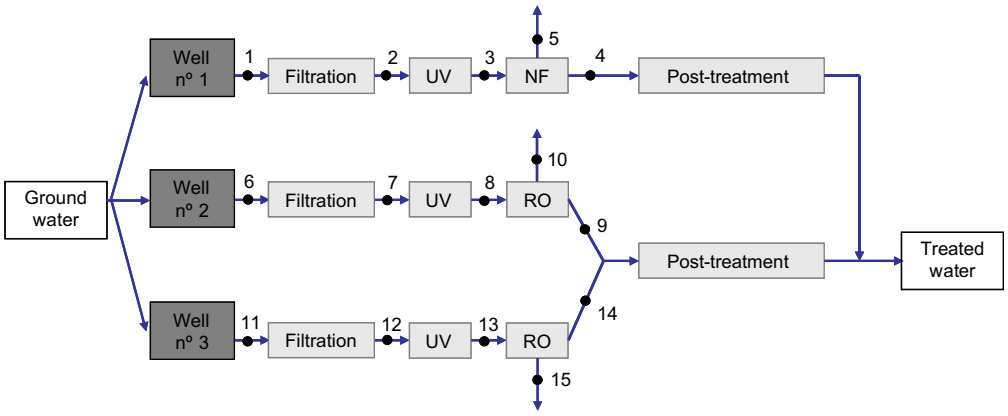


Fig. 1 – Scheme of NF and two RO treatment lines operating in parallel at the DWTP Besós, with marked sampling points: 1, 6, 11 – groundwater feed wells; 2, 7, 12 – after conditioning in pre-treatment; 3, 8, 13 – after UV radiation in pre-treatment; 4, 9, 14 – permeates of NF, RO1 and RO2 membrane unit, respectively; 5, 10, 15 – concentrates of NF, RO1 and RO2 membrane unit, respectively.

treatment step. Concentrates from NF and RO treatments are disposed downstream DWTP into the Besós River, whereas its characteristics fulfil with existing legislation requirement on concentrate disposal to surface waters.

2.3. *Sampling and sample preparation*

The three treatment lines (i.e., one NF and two RO lines) operating in parallel were sampled in five sampling campaigns conducted during the months of September (one), October (two) and November (two), 2006. The sampling points were: (1) three groundwater wells that were fed from the same central reservoir (see Fig. 1), (2) after filtration cartridges in pre-treatment, (3) after UV radiation in pre-treatment; (4) NF and RO permeates, and (5) NF and RO retentates (i.e., concentrates). Since in the September sampling campaign one of the RO treatment lines was out of order due to membrane clogging and problems with pressure, in total 70 samples were analysed (five samples per treatment line). For the sample collection amber glass bottles pre-rinsed with ultra-pure water were used. The samples were filtered immediately upon the arrival to the laboratory through 1 μm glass fibre filters followed by 0.45 μm nylon membrane filters purchased from Whatman (England). All samples were taken as 500 ml grab samples.

All target compounds were extracted in one single extraction step, according to the previously published analytical method (Gros et al., 2006). The extraction was performed by passing 500 ml of sample volume through Oasis HLB cartridges (200 mg, 6 ml) from Waters Corporation (Milford, MA), in a Baker vacuum system (J.T. Baker, The Netherlands). The cartridges were previously conditioned at neutral pH with 5 ml of methanol followed by 5 ml of deionised water (HPLC-grade). The elution was performed two times with 4 ml of methanol at a flow of 1 ml min^{-1}. The extracts were then evaporated under a nitrogen stream and reconstituted with 1 mL of methanol–water mixture (25:75, v/v).

Table 2 – Membrane characteristics and operating conditions of NF and RO membranes operating in the DWTP Besós

	NF90-400	BW30LE-440
Membrane type	Polyamide thin-film composite	Polyamide thin-film composite
Nominal surface active area (m^2)	37	44
pH range, continuous operation	3–10	2–11
NaCl rejection (%)	85–95	99
$MgSO_4$ rejection (%)	>97	100
MWCO (Da)	200	–
Operating flux (L m^{-2} h^{-1})	22.9	22.5
TMP (kg cm^{-2})	~6.0	7.3–8.7
Contact angle(°)	63.2[a]	–
Isoelectric point, pH	4.0[b]	–

a Xu et al. (2005).
b Nghiem et al. (2005).

2.4. *Chemical analysis*

LC analysis was performed using a Waters 2690 HPLC system (Milford, MA, USA) coupled to a Micromass Quattro (Manchester, UK) triple quadrupole mass spectrometer, equipped with a Z-spray electrospray interface. Chromatographic separation was achieved with a Purospher Star RP-18 endcapped column (125 × 2.0 mm, particle size 5 μm) and a C_{18} guard column, both supplied by Merck (Darmstadt, Germany). Details of specific multi-residue analytical method applied for the analysis are published elsewhere (Gros et al., 2006), with the addition of hydrochlorothiazide and glibenclamide.

Recoveries of the method were determined as follows: groundwater samples were spiked in triplicate with a standard mixture of selected compounds to a final concentration of 50 ng L^{-1}. Spiked samples together with a blank sample were analysed by the above-mentioned method. The recoveries were determined after subtraction of blank concentrations from the ones measured for spiked samples, and comparison

of the concentrations obtained (calculated by internal standard calibration) with the initial spiking levels. Recoveries of the pharmaceuticals included in the analytical method were in the range 43.6% (mevastatin)–112.3% (glibenclamide), whereas for most of the compounds they were very satisfactory (>75%). The measured concentrations of target analytes were corrected for these recoveries. Method detection limits (MDL) and method quantification limits (MQL) were determined from spiked water samples, as the minimum detectable amount of analyte with a signal-to-noise ratio (S/N) of 3 and 10, respectively. MQLs were in the range 0.2 (propyphenazone)–71.3 ng L^{-1} (ketoprofen).

3. Results and discussion

Compounds detected in all five sampling campaigns at relatively high concentrations (>100 ng L^{-1}) in groundwater and feed stream to NF and RO membrane racks were the following: a diuretic hydrochlorothiazide, analgesics and anti-inflammatory drugs (i.e. ketoprofen, diclofenac and propyphenazone), a lipid regulator pravastatin and an antiepileptic drug carbamazepine (see Table 3). Two compounds (i.e., anti-inflammatory drug mefenamic acid and hypoglycaemic agent glibenclamide) were encountered only in three sampling campaigns. Some of these pharmaceutical residues have been previously reported to be present in surface and groundwater (Seiler et al., 1999; Sacher et al., 2001; Loos et al., 2007; Holm et al., 1995). Moreover, surprisingly high concentrations were detected for hydrochlorothiazide in the first conducted sampling campaign (around 2.6 μg L^{-1} in groundwater wells). This could be explained by less frequent rainfall events during the month of September 2006, which reflected on the values for groundwater concentrations of all detected pharmaceutical residues. Also, an accidental discharge from a near-by pharmaceutical industry could have led to such discrepancy with the data obtained from other sampling campaigns. The Besós River flows through densely populated and industrial areas, receiving also effluents from the pharmaceutical companies, and is heavily polluted.

The concentrations of the encountered pharmaceuticals did not vary significantly after the conditioning stage, when compared to the ones measured in the groundwater. In some cases they were slightly increased, probably due to desorption from the filtration cartridges that are cleaned in irregular periods. Furthermore, UV radiation did not remove any of the selected pharmaceuticals, since the UV dose applied for disinfection (i.e., 400 J m^{-2}) was insufficient for a breakdown of low MW compounds (Snyder et al., 2003). The out-going stream of UV radiation stage was the feed stream to NF and RO membrane racks.

Rejection (R) of each encountered compound was calculated as:

$$R\ (\%) = \frac{C_F - C_P}{C_F} \times 100\ (\%) \quad (1)$$

where C_F and C_P are concentrations of a compound in feed stream (i.e., final effluent of the pre-treatment) and permeate, respectively. The rejections of the detected pharmaceuticals in full-scale NF and RO treatments are depicted in Fig. 2.

As systematized by Bellona et al. (2004), rejection of solute on NF/RO membranes will be affected by solute and membrane properties, feed composition and operating conditions. Solute can be rejected on NF and RO membranes by one or combination of three basic mechanisms: size exclusion (sieving, steric effect), charge exclusion (electrical, Donnan) and physico-chemical interactions between solute, solvent and membrane. The rejection of uncharged trace organics by NF and RO membranes is considered to be predominantly

Table 3 – Method quantification limits (MQLs), frequencies of detection (F), ranges and median values for concentrations of compounds detected in groundwater (GW), permeates of NF (NFp) and two RO treatment lines (ROp), and in brine (BR) of all three membrane treatments in the DWTP Besós

Compounds	MQL (ng L^{-1})	F[a] (GW, BR) ($N = 5$)	c (GW) (ng L^{-1})[b]	F (NFp) ($N = 5$)	c (NFp) (ng L^{-1})[a]	F (ROp) ($N = 9$)	c (ROp) (ng L^{-1})[a]	c (BR) (ng L^{-1})
HCTZ	0.3	5	58.6–2548 (83.5)	5	2.6–330 (7.1)	9	0.8–117 (2.8)	126–6336 (214)
KTP	71.3	5	<MQL[c]–314 (137)	1	<MQL–37 (<MQL)	2	<MQL–51 (<MQL)	132–695 (429)
GMFB	1.0	5	<MQL–496 (10.3)	3	<MQL–298 (1.1)	4	<MQL–288 (<MQL)	2.2–347 (11.8)
DCF	18.7	5	60.2–219 (121.5)	0	–	0	–	171.2–520 (250.9)
ACTP	4.3	5	<MQL–34.7 (7.6)	4	<MQL–9.3 (<MQL)	5	<MQL–16.7 (<MQL)	6.4–64.1 (19.9)
STL	0.67	5	<MQL–12.2 (4.3)	0	–	1	<MQL–3.1 (<MQL)	7.6–42.9 (21.7)
SMX	2.0	5	13.5–28.7 (21)	1	<MQL–4.8 (<MQL)	0	–	43.6–102 (66.9)
MTPL	1.0	5	9.3–56.3 (10.9)	1	<MQL–8.1 (<MQL)	2	<MQL–13.5 (2.6)	11.6–86.2 (32.6)
PPZ	0.2	5	51.5–296 (41.6)	3	<MQL–7.9 (0.6)	4	<MQL–12.0 (<MQL)	91.8–294 (155.7)
CBZP	0.3	5	8.7–167 (84.5)	5	0.5–5.7 (1.0)	7	<MQL–1.8 (1.2)	231.5–692 (352.1)
MFAC	0.3	3	<MQL–32.5 (6.2)	3	<MQL–19.9 (1.9)	4	<MQL–19.8 (0.9)	0–19.8 (0.8)
GLBC	1.33	3	<MQL–27.6 (11.7)	1	<MQL–2.9 (<MQL)	2	<MQL–2.8 (<MQL)	0–35.8 (15.9)

The acronyms stand for: HCTZ, hydrochlorothiazide; KTP, ketoprofen; GMFB, gemfibrozil; DCF, diclofenac; ACTP, acetaminophen; STL, sotalol; SMX, sulfamethoxazole; MTPL, metoprolol; PPZ, propyphenazone; CBZP, carbamazepine; MFAC, mefenamic acid; and GLBC, glibenclamide.

a F, frequency of detection.

b Concentrations are presented as a range, with median values inside the brackets.

c <MQL, below method quantification limit (MQL).

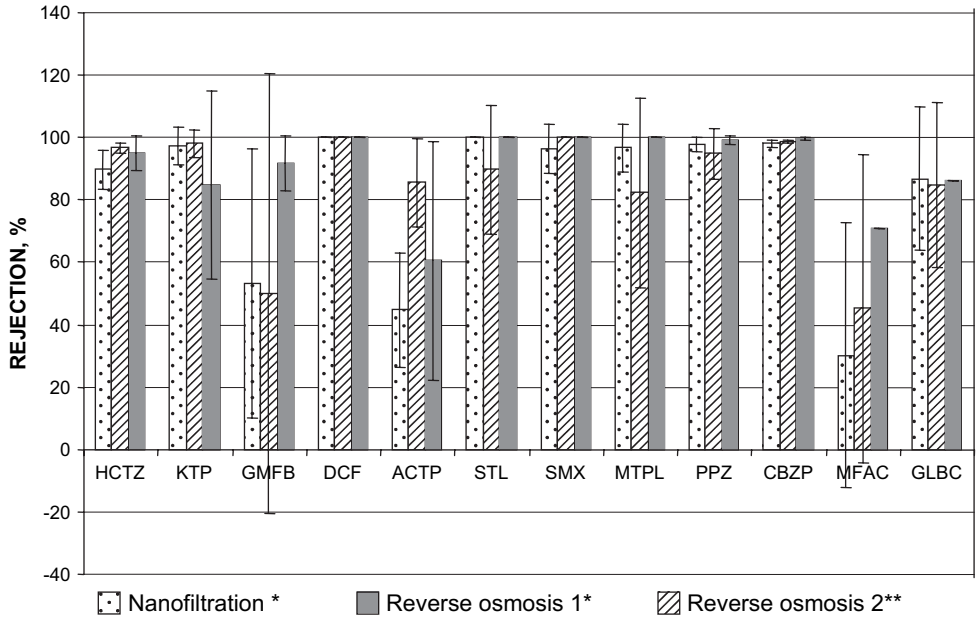


Fig. 2 – Rejection efficiencies in conditioning, UV, NF/RO stage of treatment are illustrated for the encountered pharmaceutical residues. Rejections are presented as mean values, with their corresponding RSDs for the NF and RO filtration stages, whereas *N = 5, and **N = 4 for HCTZ, KTP, GMFB, DCF, ACTP, STL, SMX, MTPL, PPZ, CBZP, and *N = 3, and **N = 2 for MFAC and GLBC.

influenced by steric hindrance (size exclusion), while the rejection of polar trace organics is mainly governed by electrostatic interactions with charged membranes (Berg et al., 1997). In the work of Nghiem et al. (2004), pore radius of NF-90 membranes was determined to be 0.34 nm, which classified them as ''tight'' NF membranes. The retention of pharmaceuticals at these membranes was reported to be dominated by steric hindrance effects (Nghiem et al., 2005). However, another study with NF-90 and RO XLE Dow FilmTec membranes reported increased rejections of negatively charged compounds on a negatively charged membrane surface (Xu et al., 2005). Moreover, rejection of negatively charged compounds on NF-90 membrane was found to be dependent on the membrane surface charge, degree of deprotonation of the compound and presence of divalent cations (Bellona and Drewes, 2005). On the other hand, according to the pure water flux, salt rejection, and rejection layer thickness, the BW30 RO membranes from Dow FilmTec (Minneapolis, MN) can be classified as ''tight'' RO membranes (Tang et al., 2006). However, salt retention on these membranes was found to be only slightly higher than on NF-90 membranes (Masson et al., 2005).

Pharmaceuticals that were present in their non-ionic forms were hydrophilic drugs carbamazepine, acetaminophen, hydrochlorothiazide and propyphenazone, and a hydrophobic compound glibenclamide. Glibenclamide is a weak acid ($pK_a = 6.3$) (Sheppard and Robinson, 1997) that was most probably present in both undissociated and anionic form. Uncharged molecules of glibenclamide could potentially adsorb onto the membrane surface and inside the pores, as it was previously demonstrated for other hydrophobic compounds (Kimura et al., 2003a; Nghiem et al., 2004; Van Der Bruggen et al., 1999; Kiso et al., 2001a,b). Therefore, molecules accumulated on the membrane surface due to size exclusion could eventually diffuse through the membrane polymer matrix towards the permeate side. For example, experiments with membrane cells showed that EDCs can adsorb and subsequently diffuse through the NF/RO membrane polymer (Nghiem et al., 2004; Ng and Elimelech, 2004; Schäfer et al., 2003). Therefore, the phenomenon of adsorption and diffusion may be a possible explanation for slightly lower rejections of glibenclamide in NF and RO treatments ($R \sim 85\%$) compared to rejections of other uncharged pharmaceuticals with MW larger than the molecular weight cut-off (MWCO) of the membranes. Also, groundwater concentrations of glibenclamide were in low nanogram per litre range (see Table 3), thus the uncertainty of evaluation of NF/RO membrane performances at such low level is increased, and could be the explanation of slightly worsened rejection.

On the other side, rejection of hydrophilic, uncharged molecules (i.e., carbamazepine, acetaminophen, hydrochlorothiazide and propyphenazone) should be enhanced, considering their greater affinity towards water and thus larger hydrated radius (Braeken et al., 2005). Considering the MWCO of the investigated NF membrane (200 Da $\sim$ 200 g mol^{-1}), all of the encountered compounds should be well rejected by the mechanism of steric hindrance except for acetaminophen (i.e., MW = 151.16 g mol^{-1}). This may explain its limited rejection on NF and RO membranes (i.e., $R = 44.8\%$ and 73.1%, respectively). Moreover, like in the case of glibenclamide, acetaminophen was detected in groundwater wells at very low concentrations (i.e., <MQL–34.7 ng L^{-1}). Carbamazepine had an excellent removal in NF and RO treatments ($R > 98\%$). This was in accordance with results from full-scale applications of RO membranes (Snyder et al., 2007; Al-Rifai et al., 2007), while some previous laboratory-scale studies report

diverse retentions of carbamazepine on NF/RO membranes (i.e., 10–91%) (Nghiem et al., 2006; Amy et al., 2005; Kimura et al., 2004). Nevertheless, a pilot-scale study of Bellona and Drewes (2007) showed 95% rejection of carbamazepine on FilmTec
NF-4040 membranes at 700 ng L^{-1} spiking level, whereas no retention of uncharged acetaminophen was observed. As far as propyphenazone is concerned, it was also highly rejected (i.e., $R \geq 97\%$). Hydrochlorothiazide with pK_a value of 7.9 for sulphonamide group was in undissociated state as well, and its mean rejections in NF and RO membrane treatment were 90% and 96%, respectively. Therefore, sieving of hydrophilic pharmaceutical residues present as neutral molecules turned out to be an efficient way of their rejection on NF/RO membranes.

Speciation of molecules, i.e. changing of their charge as a function of pH, will significantly influence their rejection on membranes. Charge for most of the thin layer composite NF and RO membranes in neutral solutions is negative, due to the dissociation of sulfonic and carboxylic groups on the membrane's skin. For example, isoelectric point of NF-90 membrane is around pH 4 (Nghiem et al., 2005). Therefore, increased rejection of negatively charged solutes could be expected due to electrostatic repulsion with membrane surface (Xu et al., 2005; Nghiem et al., 2006).

Based on their $\log K_{OW}$ values (i.e., $3 < \log K_{OW} < 5$), ketoprofen, diclofenac, mefenamic acid and gemfibrozil can be considered as moderately hydrophobic in their neutral form. However, since they were ionised at the operating pH (i.e., pH 5.6–6.1) of NF and RO membrane racks, their hydrophobicities were significantly lowered. Ketoprofen and diclofenac had excellent rejections in both NF and RO ($R > 95\%$), similar to previously reported results from full-scale RO (Al-Rifai et al., 2007). In pilot-scale testing of Dow/FilmTec NF-4040 membranes, rejection of these two pharmaceuticals was reported to be practically 100 % (Bellona and Drewes, 2007). Also, in laboratory-scale cross-flow tests with NF-90 membranes (Xu et al., 2005; Amy et al., 2005) rejections of ketoprofen and diclofenac were reported to be greater than 90%. In another study with RO membranes the retention of negatively charged diclofenac was 95% (Kimura et al., 2003b). Nevertheless, rejections of other two anionic drugs gemfibrozil and mefenamic acid were slightly deteriorated (i.e., 50–70% and 30–50%, respectively). Moreover, mefenamic acid mostly permeated NF membranes (only 30% removal). However, for this compound mean rejections were calculated based on only three positive findings and with great variations between them. Moreover, feed stream concentrations of mefenamic acid were very low (i.e., <MQL–21.8 ng L^{-1}), which could be the reason for the decrease in rejection efficiency (Kimura et al., 2003b). Also, Ca^{2+} ions that were present in feed water at approximately 140 mg L^{-1} concentration could have lowered the membrane surface charge, and thus influence the retention of some negatively charged pharmaceuticals (Bellona and Drewes, 2005; Nghiem and Schäfer, 2006). Bellona and Drewes (2005) reported 20–25% reduction of effective membrane surface charge in the presence of divalent cations (i.e., 120 mg L^{-1} Ca^{2+}).

In some previous studies, polar (lower $\log K_{OW}$) and charged compounds were found to have a better removal in NF/RO processes due to interactions with membrane surfaces (Bellona et al., 2004; Braeken et al., 2005; Amy et al., 2005; Ozaki and Li, 2002). Kim et al. (2007) explained the enhanced rejection of hydrophilic charged compounds as a consequence of convection dominated transport of molecules. Among the pharmaceuticals that were present in their charged state, sulfamethoxazole, atenolol and metoprolol represent hydrophilic drugs. Sulfamethoxazole possesses two ionisable amine groups and it can carry a positive, neutral or negative charge (Nghiem and Schäfer, 2004). Considering its experimental value for the second ionization constant (i.e., pK_{a2} 5.6) (see Table 1), and the pH of the entering water, sulfamethoxazole will probably be present as both uncharged and negatively charged molecule. In full-scale DWTP mean rejections of sulfamethoxazole on NF and RO membranes were 96.4% and 100%, respectively. Such high efficiency of membranes was probably a result of combination of size exclusion mechanisms and repellent electric force between the solutes and the membrane. Nevertheless, around 95% retention of uncharged sulfamethoxazole was reported for FilmTec NF-4040 membrane operating at a pilot-scale (Bellona and Drewes, 2007). On the other hand, ß-blockers sotalol and metoprolol were protonated at the operational pH, whereas for these two pharmaceuticals very high NF and RO rejections were observed (i.e., $R > 90$ %). This is somewhat surprising since these positively charged ions could be expected to accumulate on negatively charged membrane and diffuse through it more easily (Verliefde et al., 2007). Nevertheless, Verliefde et al. (2007) observed better rejections on NF membranes of positively charged pharmaceuticals present at higher concentrations, which were hypothesized to be due to shielding effect of accumulated positive ions on the membrane surface that lower the intensity of electrostatic attraction, and enhance their rejection. In our study, high rejection rates of the two detected ß-blockers can possibly be explained by steric effects, considering the MWCOs of the NF and RO membranes.

On the other side, both NF and RO treatment generate a large amount of concentrated waste stream as a by-product in the DWTP Besós. Results reported in Table 3 indicate that the output of a DWTP was brine with most of the encountered pharmaceutical at concentrations of several hundreds nanogram per litre. These concentrates are being discharged into the near-by river. However, since they represent only 1% of the river water flow the dilution effect is considered adequate enough for minimizing their environmental impact.

4. Conclusions

The mechanism of size exclusion brought about very high rejections (i.e., >85%) for uncharged solutes of carbamazepine, hydrochlorothiazide, propyphenazone and glibenclamide that have MW greater than the MWCO of NF/RO membranes, whereas in the case of acetaminophen the retention was lowered (i.e., 44.8–73%), probably due to its small molecular size (i.e., MW < MWCO). The highest rejections in NF/RO processes were recorded for negatively charged pharmaceuticals ketoprofen, diclofenac, and sulfamethoxazole ($R > 95\%$). On the other side, negatively charged gemfibrozil and mefenamic acid were removed on NF and RO membranes

with relatively poor efficiency (i.e., 50–70% and 30–50%, respectively), for which no plausible explanation was found. Finally, positively charged sotalol and metoprolol were retained on the membranes with very high efficiency ($R > 90\%$).

The study proved NF and RO membranes applied in a full-scale DWTP to be very efficient in removing nearly all of the pharmaceutical residues detected. Furthermore, the presence of many pharmaceuticals at substantial concentrations in the brine stream has been confirmed. Although the characteristics of brine comply with the existing regulations in Europe on dumping the residual water into surface water, the release of non-regulated contaminants such as pharmaceuticals could represent a matter of concern.

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