An integrated approach for the management of pharmaceutical products in environmental waters

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Abstract

At a time when water resources become impoverished, it becomes necessary to keep water supplies under surveillance and to preserve them from any contamination due to either known pollutants (priority substances listed in the Water Framework Directive) or emerging ones. Pharmaceutical products (PPs) are emerging pollutants of interest as they can be still biologically active in waterways and could impact aquatic ecosystems. They actually contaminate surface and groundwater through direct runoff or discharge of treated sewage where they are not completely eliminated. Moreover, some compounds have been found in drinking water.
An integrated approach which considers the whole life-cycle of PPs is proposed to identify the main pressure points and then to propose actions enable to reduce their occurrence and their impact on the aquatic environment.
For this purpose, an environmental typology of PPs is developed according to different criteria (treatment plant characteristics, amount of treated wastewater per inhabitant and per day, origin of the sewage, …) and draw a state of occurrence of PPs toward these criteria. In this frame, sampling campaigns have been carried out and PPs have been analyzed by LC-MS/MS. In parallel, several additional treatments (photo-oxidation, adsorption) are tested for the elimination of traces of PPs in environmental waters. All the data will be inter-connected and results will be scrutinized in order to propose actions for lowering occurrence and impact of pharmaceuticals in water supplies. This work is in support for KNAPPE (Knowledge Assessment of Pharmaceutical Products in Environmental waters) project, funded by European Commission (Specific Support Action - contract n° 036864).

Keywords

Pharmaceutical products, integrated approach, environmental typology, water management

1. Introduction

At a time when water resources become impoverished, it becomes necessary to keep water supplies under surveillance and to preserve them from any contamination due to either known pollutants (priority substances listed in the Water Framework Directive) or emerging ones. Pharmaceutical products (PPs) are widely used chemicals. They are excreted with urine or faeces to raw sewage in both an unchanged form and as metabolites. Since 1980's, the presence of pharmaceuticals was reported in a lot of studies in Europe (Garric and Ferrari, 2005; Kummerer, 2004; Nikolaou et al., 2007). With the improvement of detection methods, low levels of PPs were detected in surface water (Gros et al., 2006; Paffoni et al., 2005; Togola and Budzinski, 2007) and groundwater (Ellis, 2006; Rabiet et al., 2006). Recent studies have demonstrated that elimination of many pharmaceuticals in sewage treatment plants (STP) is often incomplete (Castiglioni et al., 2006; Gros et al., 2007; Jones et al., 2005; Joss et al., 2005; Ternes et al., 2005; Ternes, 1998).

As PPs permanently enter waterways where they can be still biologically active, they should be considered as emerging pollutants of interest. They are persistent pollutants and could impact aquatic ecosystems (Cleuvers, 2003; Crane et al., 2006; Webb, 2004). Moreover, some compounds have been found in drinking water (Stackelberg et al., 2007).

In this context, the European KNAPPE (www.knappe-eu.org) proposes an integrated approach relying on the whole lifecycle of pharmaceutical products (PPs) from manufacture to exposure (Figure 1) (Coetsier et al., 2007)

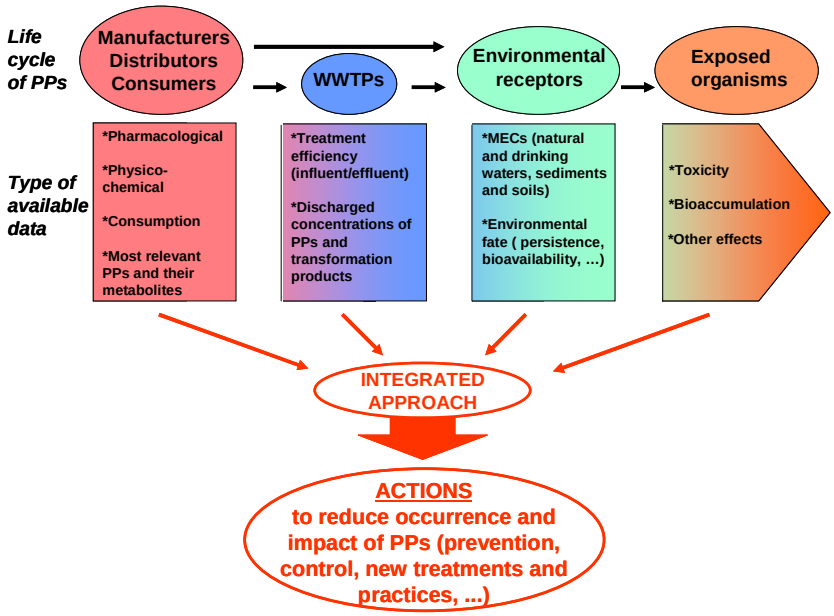

Figure1 Integrated approach considering the whole life-cycle of PPs (Coetsier et al., 2007)

As a contribution to this far-reaching project, the aims of the present study were:
(1) To identify pharmaceutical compounds in some of the sewage treatment plants (STP) of the south-eastern France. For this purpose, sampling campaigns have been carried out and PPs analyzed by LC-MS/MS.
(2) To test tertiary treatments as potential actions wich could be done to reduce occurrence of PPs in surface waters. In this study, photo-oxidation and adsorption were considered.

2. Material and methods

2.1. Sampling sites

Seven wastewater treatment plants (South-eastern of France) have been investigated. Sampling sites were chosen regarding the STP characteristics (Table 1):

- Served population (equivalent habitant),
- Daily flow rate and origin of sewage (domestic, industrial, hospital),
- Treatment process.

24-h averaged flow proportional samples of effluents were collected from June 2007 to April 2008 for each STP. Samples were stored at cooled temperature (4°C) before to be treated at laboratory on the same day.

Table 1 Characteristics of investigated STP

	STP 1	STP 2	STP 3	STP 4	STP 5	STP 6	STP 7
Served population (EqHab)	3000	55000	100000	650000	24000	100000	800
Median flow rate (m3/j)	130	11000	9300	220000	1500	3000 winter / 8000 summer	110
influent BOD_5 mg $O_2.L^{-1}$	300	300	300	170	-	-	250
Received sewage	Domestic	Domestic Industrial Hospital	Domestic Industrial Hospital	Domestic Industrial Hospital	Domestic Industrial Hospital	Domestic Industrial Hospital	Domestic
Treatment processes	Primary settling Activated sludge Nitrification-denitrification Low load	primary settling activated sludge Nitrification-denitrification, Phosphate removal Low load	Primary settling Biotrickling Nitrification Biofilter Phosphate removal Low load	Primary settling activated sludge High load	primary settling activated sludge Nitrification-denitrification, Phosphate removal, membrane bioreactor Low load	primary settling activated sludge Nitrification-denitrification, Phosphate removal Low load	Macrophytes-based lagoon
Receiving medium	River	River	River	Sea	River	Lagoon, sea	River

2.2. Chemicals

Eleven PPs have been analyzed. Standard products were purchased from Sigma–Aldrich (purity > 97% by weight, CAS no. indicated): norfloxacin (70458-96-7), acebutolol (34381-68-5), propranolol (318-98-9), ifosfamide (3778-73-2), pravastatin (81131-70-6), carbamazepine (298-46-4), lorazepam (846-49-1), tamoxifen (10540-29-1), diclofenac (15307-79-6), ibuprofen (15687-27-1) and fenofibrate (49562-28-9). The list of pharmaceuticals considered in this study was selected on the basis of the leading medicinal products most frequently encountered in French surface waters (Andreozzi et al., 2003) and most consumed in France. Solvents, acetonitrile, methanol, ethyl acetate, acetone and 0.1 % acetic acid water of gradient grade were purchased from Chromasolv, Riedel-de-Haen. Standard solutions have been made in a 50:50 mixture methanol:milliQ pure water.
Figure 2 shows the molecular structure of the PPs investigated in this study. Table 2 gives more details about some characteristics of PPs as molecular weight (MW), log Kow and pKa.

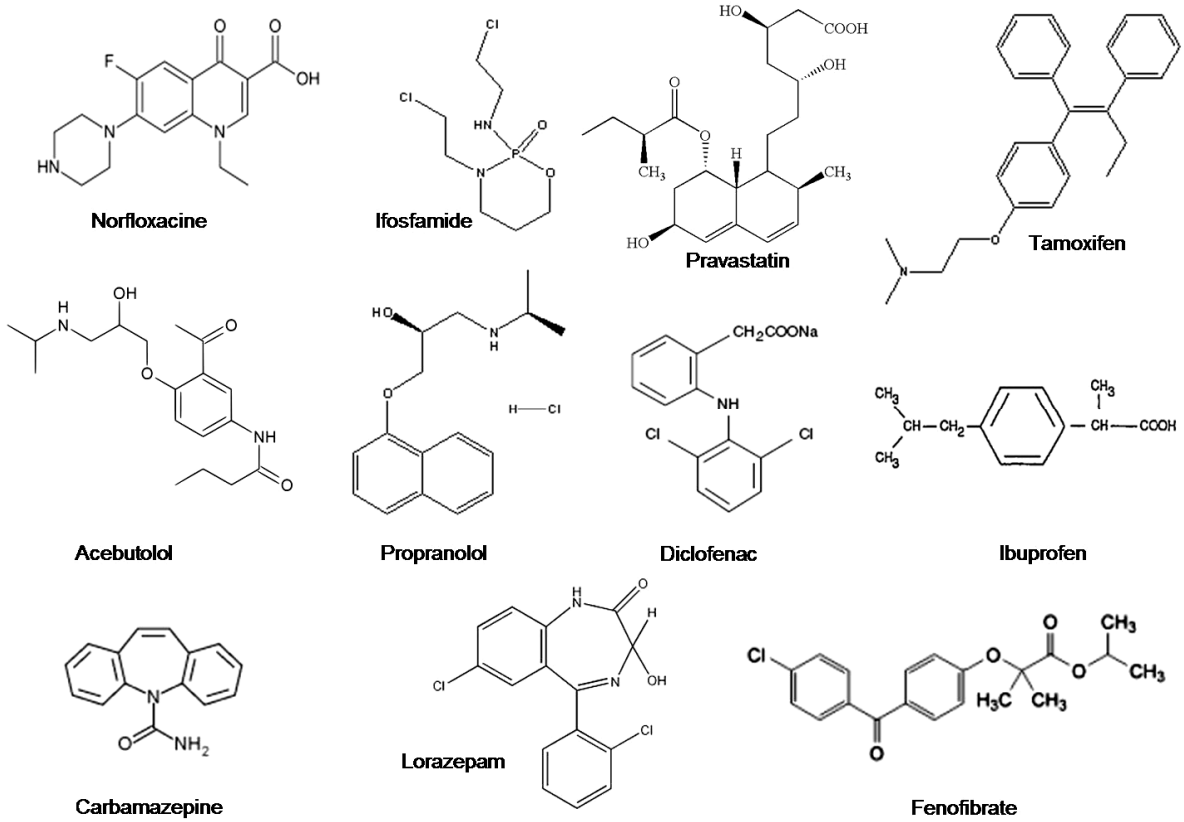

Figure 2 Molecular structures of the investigated PPs

Table 2 Characteristics of PPs

Compounds	*Therapeutic class*	MW ($g.mol^{-1}$)	Formula	Log Kow	pKa
Norfloxacin NOR	*Fluoroquinolone antibiotic*	319,3	$C_{16}H_{18}FN_3O_3$	-1,03a, -0,31**	-
Acebutolol ACE	*β-blockers*	336,4	$C_{18}H_{28}N_2O_4$	1,71a	-
Propranolol PROP		259,8	$C_{16}H_{22}ClNO_2$,HCl	0,74**,-0,45d	9,45d
Ifosfamide IFO	*Antineoplastic*	261,1	$C_7H_{15}Cl_2N_2O_2P$	0,86a	-
Pravastatin PRAV	*Statin lipid regulator*	446,5	$C_{23}H_{35}NaO_7$	-0,23a, -0,71**	-
Carbamazepine CAR	*Anti-convulsivant*	236,3	$C_{15}H_{12}N_2O_7$	2,45a, 2,93b, 2,25c,**	7b 13,9c ;
Lorazepam LOR	*Anxiolytic*	321,2	$C_{15}H_{10}Cl_2N_2O_2$	2,39a, 2,41**	13 ; 11,5
Tamoxifen TAM	*Anticancer agent SERM**	371,5	$C_{26}H_{29}NO$	6,3**	-
Diclofenac DIC	*Antiflogistics*	318,1	$C_{14}H_{10}Cl_2NNaO_2$	0,7b,, 0,57**	4,15a, 4,2b
Ibuprofen IBU		206,3	$C_{13}H_{18}O_2$	3,99a, 3,14b, 3,5c, 3,79**	5,2b, 4,9c
Fenofibrate FEN	*Fibrate lipid regulator*	360,8	$C_{20}H_{21}ClO_4$	5,19**	-

* *Selective Estrogen Receptor Modulator*
** ECOSAR prediction
a: Syracuse research Corporation Databases (http:// esc.syrres.com)
b: (Jjemba, 2006)
c: (Jones et al., 2002)
d: Hazardous Substances Databank (HSDB), National Library of Medicine, Specialized Information Services. Retrieved 2004 - 2005 from http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

2.3. Analytical method

SPE extraction

Solid phase extraction was performed on GF/F glass-filtered acidified wastewater samples (500 mL) using STRATA X cartridges (Phenomenex, Inc., France). The cartridges were flushed with milliQ water (pH 2), dried under nitrogen flow. Analytes were eluted with 5 ml of ethyl acetate followed by 5 ml of a 50:50 (v/v) mixture ethyl acetate:acetone and finally 5 ml of a 49:49:2 (v/v/v) mixture ethyl acetate:acetone:ammonium hydroxyde. After removal of the excess solvent(s) under nitrogen flow, the volume was brought to 0.5 ml using methanol.
Extracts from unspiked ultra-pure grade water, concentrated and treated as described above, were used as blanks.

LC-MS/MS

Analysis of pharmaceuticals was performed using LC–MS/MS. The LC system consists of Separations module Alliance HPLC Waters 2695 equipped with a quaternary pump, a vacuum degasser and an autosampler. Chromatographic separation was performed on Ascentis C18 (50 mm x 2.1 mm, 3 µm) reversed-phase column, packed with silica and octadecyl bonded-phases (Supelco, UK). Chromatographic conditions were as follows:

- solvents A A (H_2O; 0,1% HCOOH) and B (CH_3CN),
- flow rate 0,4 $ml.min^{-1}$
- gradient program (Table 3).

Table 3 Gradient solvent program

Time (min)	Solvent A	Solvent B
0	85	15
8	50	50
13	30	70
15	0	100
17	0	100
18	85	15
25	85	15

The mass-spectrometric detection was performed on micromass Quattro micro™ (Waters) equipped with electrospray, using multi-reaction monitoring (MRM) mode detecting the daughter ions of m=z.
Characteristics of the analytical method are presented in Table 4.

Table 4 Analytical method performances

Compounds	**SPE recovery (%)**	**Limits of detection ($ng.L^{-1}$)**	**Limits of quantification ($ng.L^{-1}$)**
NOR	47 ± 5	5,2	12
ACE	73±3	2,8	8,5
PROP	80 ± 8	2	9,6
IFO	94±7	2,8	9,7
PRAV	38±2	7,7	19
CAR	93±12	0,4	0,8
LOR	84±4	1,3	4
TAM	71 ± 4	5,8	14
DIC	80 ± 8	0,7	2
IBU	53 ± 4	0,3	0,5
FEN	71 ± 6	5,5	12

For the majority of PPs, the absolute recoveries obtained in this study are sufficiently high (>60%) and are in agreement with the previously published data (Hilton and Thomas, 2003). Recoveries less than 60 % for norfloxacin (47 %), pravastatin (38 %) and ibuprofen (53 %),

were all sufficiently high and reproducible (R.S.D. < 10 %) to be used for environmental monitoring.

The detection using LC-MS/MS in MRM mode resulted in a low noise level of the baseline and improved sensitivity (Andreozzi et al., 2003). This was particularly important for analysis of the pharmaceuticals in the real wastewater samples (Petrovic et al., 2005).

2.4. Tertiary treatments

UV photolysis and adsorption on powdered activated carbon (PAC) have been assessed to eliminate pharmaceutical products.

Experiments were conducted with individual PPs solutions (100 µg.L^{-1}), prepared in milliQ water to compare the sensitivity of compounds toward UV photolysis and adsorption. Then, solutions of PP were prepared in effluent sample (STP2) to assess influence of this complex matrix on the treatments efficiency. STP2 effluent is characterized by COD (Chemical Oxygen Demand) and TSS (Total Suspended Solids) concentrations, ranging respectively from 30 to 36 mgO_2.L^{-1} (COD) and 5 to 12 mg.L^{-1} (TSS) on the tests duration.

For adsorption, 300 mL of solutions are shacked up with 50 g/L of PAC (PICA Society, France). For photolysis, 5 L of solutions are circulated under low pressure Hg UV lamp (254 nm, 11-15 mW/m²) with irradiation time of 20 sec by pass (flow rate: 1.2 L.min^{-1}). The UV lamp emission spectrum is given in Figure 3. The main irradiation wavelength is located at 253.6 nm; another wavelength occurs in vacuum UV (184.9 nm).

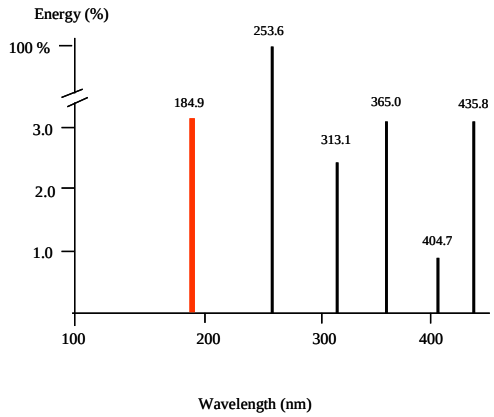

Figure 3 Low pressure Hg UV lamp emission spectrum

The removal of PPs was assessed by direct LC-MS/MS analysis.

3. Results and discussion

3.1. Occurrence of pharmaceuticals in STPs effluent

Concentrations of pharmaceuticals found in this study are presented in Table 5. Literature data for some other French STP are joined.

Data from these campaigns show that 5 compounds are predominant in studied effluents: acebutolol, propanolol, carbamazepine, diclofenac and ibuprofen. The range of concentrations varies from 100 ng.L^{-1} to 1.5 µg.L^{-1}. On the whole, these results are in accordance with

concentrations in Rhône-Alpes effluents STPs reported by (Andreozzi et al., 2003; Paffoni et al., 2005). Nevertheless, it can be noticed that higher concentrations of ibuprofen (Rhône Alpes STP1) have been found. This drug is highly prescribed and widely used in France.
Diclofenac and ibuprofen investigated by Togola and Budzinski, 2008 in Herault effluent STP are found in the same order of magnitude. Carbamazepine has been detected at lower concentration in Herault effluent STP.

Some of the PPs studied in this work (lorazepam, tamoxifen and ifosfamide) have, to the best of our knowledge, not been reported previously in French STP effluents. Lorazepam has been found in all the studied STPs at a concentration of dozens of $ng.L^{-1}$. Tamoxifen is present too, mostly at lower concentration. Ifosfamide and pravastatin concentrations are, most of the time, under the detection limit.

Considering STPs performances, lagoon process (STP7) seems to be less efficient to eliminate PPs than activated sludge process.

Table 5 Minimal-maximal values measured in the studied STP effluent samples expressed in ng.L^{-1} (nd: not detected).

	STP 1 (n*=2)	**STP 2 (n=8)**	**STP 3 (n=2)**	**STP 4 (n=1)**	**STP 5 (n=1)**	**STP 6 (n=1)**	**STP 7 (n=2)**	Herault eff. STP (Togola and Budzinski, 2008)	Ile de France eff STP (Paffoni et al., 2005)	Rhône-Alpes eff. STP1 (Andreozzi et al., 2003)	Rhône-Alpes eff. STP2 (Andreozzi et al., 2003)
NOR	33-45	<5.2-247	<5.2-96	144	-	236	41-187	-	-	50	50
ACE	70-93	82-192	146-900	213	266	134	394-733	-	-	130	80
PROP	390-675	179-560	84-276	-	166	281	248-1607	-	190	10	40
IFO	<2.8	<2.8	<2.8-52	<2.8	6	<2.8	<2.8	-	-	-	-
PRAV	<7.7	<7.7	<7.7-164	35	<7.7	<7.7	15-214	-	-	-	-
CAR	166-460	326-1573	323-391	326	795	256	132-895	157-293	1020	980	1200
LOR	34-41	31-196	17-65	25	63	33	10-43	-	-	-	-
TAM	<5.8	<5.8-102	<5.8-67	<5.8	7	<5.8	<5.8-40	-	-	-	-
DIC	278-315	148-409	264-436	156	418	675	112-732	211-486	810	410	250
IBU	2-439	23-67	20-443	269	87	78	224-962	18-219	600	1820	20
FEN	<5.5-27	<5.5-46	21-127	42	24	<5.5	14-27	-	310	120	20

*: sampling number

3.2. Removal of pharmaceuticals by tertiary treatments

As conventional wastewater treatments are unable to completely eliminate some of the recalcitrant PPs, it is necessary to consider additional advanced treatment technologies. Available tertiary treatment processes, such as filtration (sand filter), disinfection, ozonation, powedered activated carbon addition, tight membrane filtration (nanofiltration or reverse osmosis), have been investigated to improve the removal of persistent organic compounds (Ikehata et al., 2006; Larsen et al., 2004; Ternes et al., 2003; Westerhoff et al., 2005; Zwiener, 2007).

In this study, UV photolysis and adsorption on PAC have been tested with synthetic and wastewater spiked solutions (100 $\mu g.L^{-1}$).
Figure 4 shows the results obtained for investigated PPs in pure water. Most of them are removed within 20 seconds of irradiation time (>95 %), with the exception of fenofibrate (85 %) and norfloxacin (70 %).
The addition of 50 $mg.L^{-1}$ of powdered activated carbon is efficient to eliminate at least 80 % of studied PPs within 10 minutes of contact. Among the less adsorbed PPs, are the most lipophilic ones (norfloxacin, ifosfamide, propanolol). Despite their high value of log Kow, tamoxifen and fenofibrate are not so well eliminated by PAC adsorption (60 %, 80 % for 10 minutes of contact).

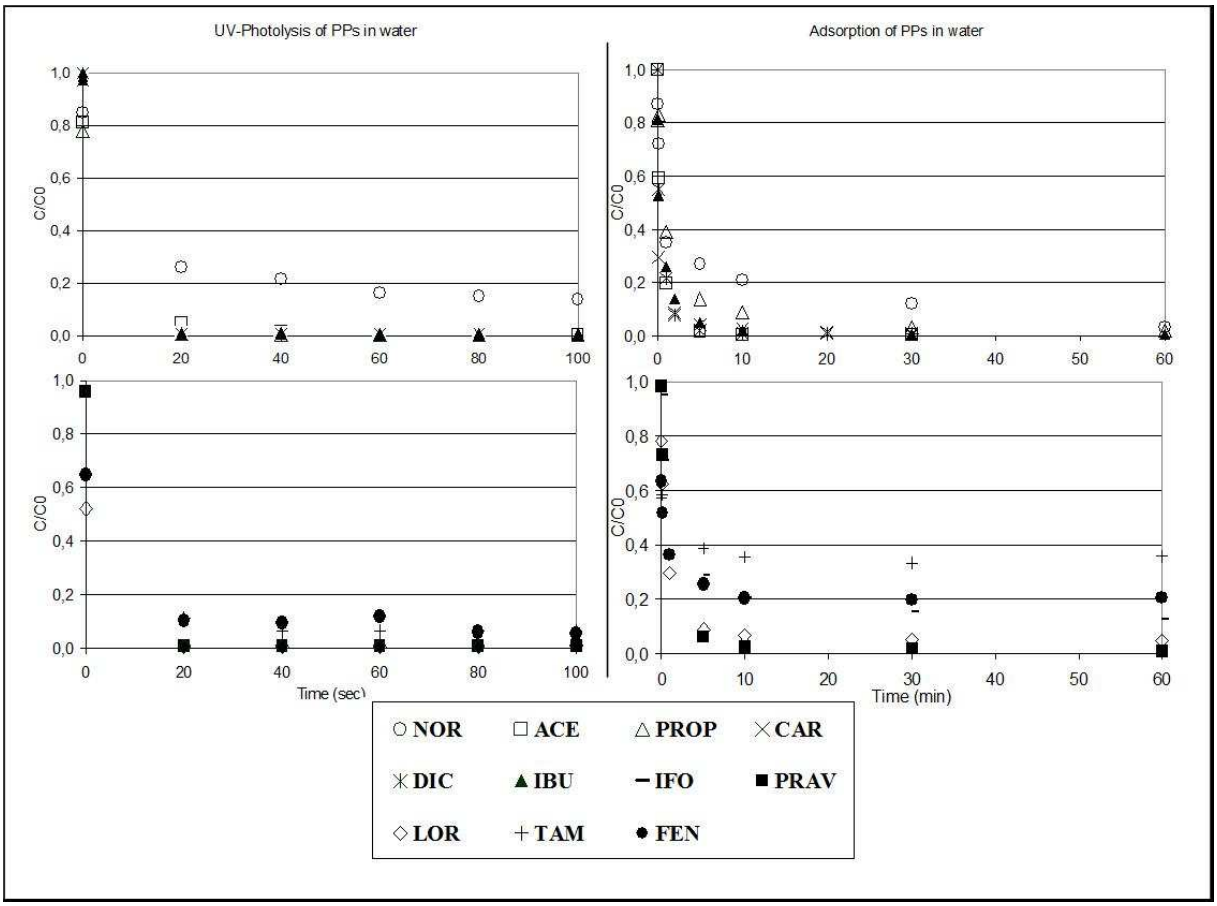

Figure 4 UV photolysis and PAC adsorption of PPs in water

Figure 5 presents the results obtained with spiked STP2 effluent. The effluent matrix obviously affects the both treatments efficiency.
UV photolysis kinetic is slowed down for all the investigated PPs. The efficiency is severely reduced for ifosfamide, lorazepam, ibuprofen, carbamazepine and acebutolol: less than 50 % of the concerned PPs are removed in 20 s irradiation.

Concerning PAC adsorption experiments, the effect of the matrix is moderate for most of the PPs. Nevertheless, the elimination of ibuprofen is reduced to 50 % for 10 minutes of contact. Adsorption of diclofenac and pravastatin is reduced to 80 % by the presence of the effluent matrix against 100 % of removal in water within 10 minutes.

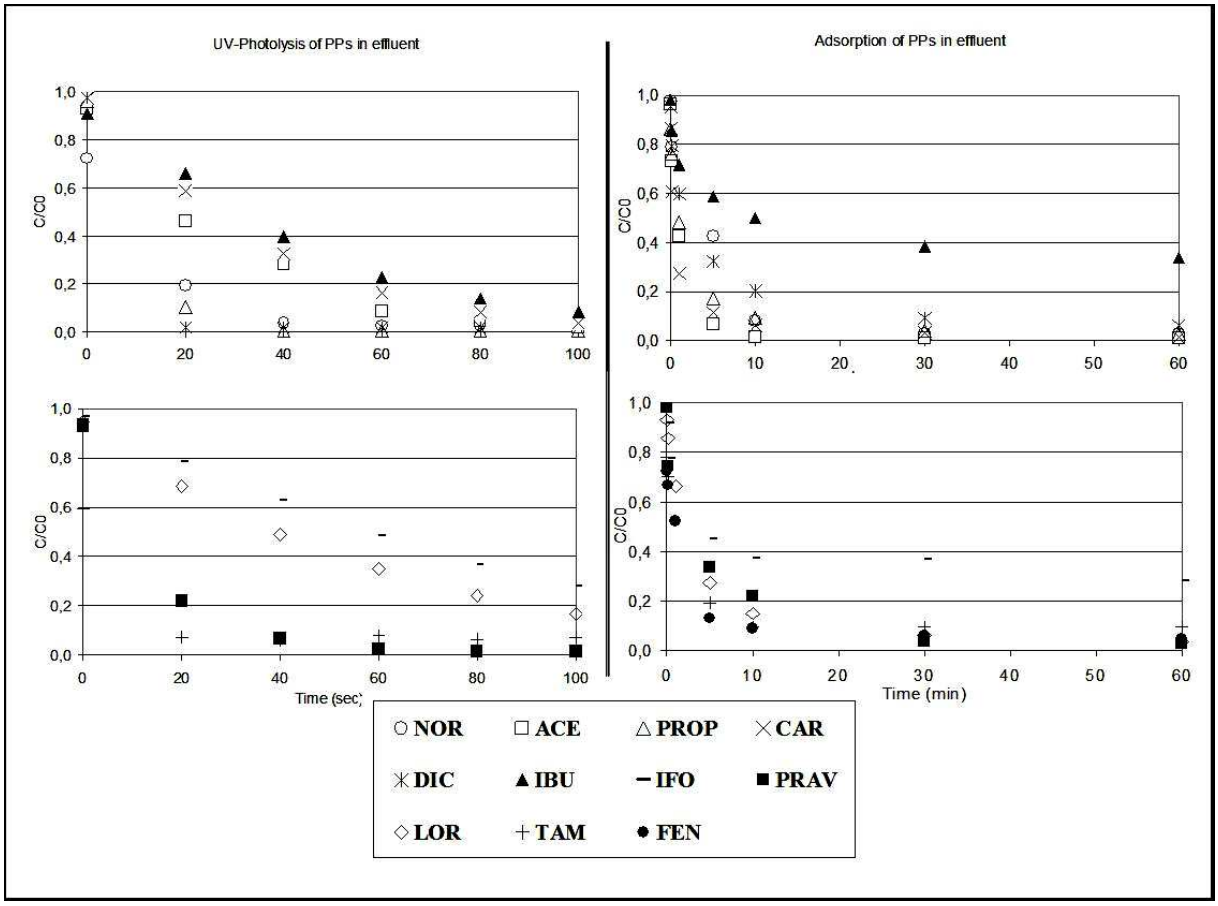

Figure 5 UV photolysis and PAC adsorption of PPs in STP2 effluent

This work shows that it is necessary to experiment the treatments of PPs in environmental matrices. UV photolysis or adsorption on activated carbon could be considered as potential tertiary treatments to prevent contamination of water resources by pharmaceuticals products. In order to improve the PPs removal efficiency in wastewater, irradiation time could be extended and PAC dose supplemented (Pereira et al., 2007a; Pereira et al., 2007b; Westerhoff et al., 2005).

4. Conclusion

This study, focussing on south eastern sewage treatment plants, contributed to improve the knowledge of pharmaceutical products occurrence in French environmental waters. Eleven drugs have been investigated, among which lorazepam, pravastatin, tamoxifen and ifosfasmide for which no data are available in France, to the best of our knowledge. Lorazepam has been detected in all the studied STP effluents at rather high concentrations (10 to 200 $ng.L^{-1}$). Tamoxifen, pravastatin and ifosfamide have been found sporadically. When detected, tamoxifen and pravastatin concentrations reached a few hundred $ng.L^{-1}$.
Among the studied biological sewage treatment plants, some of them are equipped with the last technologies: membrane bioreactor (STP5) and biofilter (STP3). These specific processes

do not seem to improve the removal of pharmaceuticals. As tertiary treatments, adsorption on activated carbon and UV photolysis have been shown to be able to eliminate several pharmaceuticals such as norfloxacin, propanolol, diclofenac among which the two last ones are predominant in the studied STPs. Tamoxifen, too, is correctly eliminated by both treatments.
Finally, carbamazepine, acebutolol and ibuprofen which are predominantly detected in wastewater treatment plant effluents seem to be the most recalcitrant to tertiary treatments, in the present experimental conditions. Furthermore, these drugs are highly dispensed in France.
The integrated approach developed within KNAPPE project will widen the field of knowledge about pharmaceuticals in the environment and should propose alternative and relevant actions especially for persistent pharmaceutical products.

Acknowledgements

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