Oxidation of pharmaceuticals by chlorine dioxide in biologically treated wastewater

Hey, G.; Grabic, R.; Ledin, Anna; la Cour Jansen, J.; Andersen, Henrik Rasmus

Published in:
Chemical Engineering Journal

Link to article, DOI:
10.1016/j.cej.2012.01.093

Publication date:
2012

Oxidation of pharmaceuticals by chlorine dioxide in biologically treated wastewater

G. *Hey*[a,*], *R. Grabic*[b], *A. Ledin*[a,c], *J. la Cour Jansen*[a], *H.R. Andersen*[c]

[a] Water and Environmental Engineering, Department of Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden

[b] Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden

[c] Department of Environmental Engineering, Technical University of Denmark, Miljøvej, Building 113, DK-2800 Kongens Lyngby, Denmark

*Corresponding author: Gerly Hey, Phone: +46 46 222 8998; fax: +46 46 222 4526
Email: gerly.moradas@chemeng.lth.se

Abstract

Biologically treated wastewater spiked with a mixture of 56 active pharmaceutical ingredients (APIs) was treated with 0-20 mg/L chlorine dioxide (ClO_2) solution in laboratory-scale experiments. Wastewater effluents were collected from two wastewater treatment plants in Sweden, one with extended nitrogen removal (low COD) and one without (high COD). About one third of the tested APIs resisted degradation even at the highest ClO_2 dose (20 mg/L), while others were reduced by more than 90% at the lowest ClO_2 level (0.5 mg/L). In the low COD effluent, more than half of the APIs were oxidized at 5 mg/L ClO_2, while in high COD effluent a significant increase in API oxidation was observed after treatment with 8 mg/L ClO_2. This study illustrates the successful degradation of several APIs during treatment of wastewater effluents with chlorine dioxide.

Keywords: Pharmaceuticals; Chlorine dioxide; Wastewater effluent

1. Introduction

One of the pressing problems in wastewater treatment plants (WWTPs) is the inability of conventional methods to completely remove active pharmaceutical ingredients (APIs) due to their high resistance to biodegradation and/or limited biological activity, especially in cold climates such as that in Sweden [1,2]. The extensive usage and hence release of traces of many pharmaceuticals in wastewater effluents may lead to surface and groundwater contamination compromising the aquatic ecosystem and the environment [3,4].

Where biological treatment is not sufficient, improvement in WWTPs can be achieved by an additional chemical oxidation step to remove potential pollutants that cannot be degraded biologically [5,6,7,8]. Among the chemical oxidants applied in water treatment reported in the literature, chlorine dioxide is one that merits further investigation regarding its potential to remove APIs in wastewater. As in the case of ozonation, the application of chlorine dioxide to treat drinking water, surface water and wastewater effluents has shown promising results for the removal of pharmaceuticals. The non-steroidal anti-inflammatory drug diclofenac, reported as one of the most frequently detected compounds in water at concentrations up to the μg/L level [9], is among the pharmaceuticals completely degraded during drinking

and surface water treatment at the lowest ClO_2 dose applied [10]. In wastewater effluents, steroid estrogens and industrial estrogenic chemicals, as well as personal care products, were removed by low doses of ClO_2 between 1.25 and 3.75 mg/L, and the removal of estrogenic potency was observed at the same time [11]. The removal of several antibiotics found in water has also demonstrated the ability of ClO_2 as an oxidant [12,13].

When ClO_2 was used for selective oxidation of organic micropollutants in other investigations on biologically treated wastewater, it was found that smaller doses, e.g. up to 4 mg/L (depending on the concentrations tested and the matrix) were consumed in less than a minute through reactions with the soluble components in the water, while still completely removing many of the reactive micropollutants. This fast consumption of the oxidant in wastewater has been observed in previous studies by Andersen [11], Hey et al. [14], Lee and von Gunten [6] and Andersen et al. [15]. Based on ClO_2 reactivity in wastewater effluents, it has been suggested that ClO_2 could be used as an alternative to ozone for the removal of micropollutants. It is easy to introduce a ClO_2 dosing step in a WWTP since ClO_2 is produced as a solution in water by mixing aqueous solutions of the reactants in a simple reactor; furthermore, the ClO_2 stock solution is semi-storable. This is much simpler than treatment with ozone, which requires on-site delivery of dry oxygen and considerable electric power to run an expensive and complicated ozone generator which produces an ozone gas mixture with less than 20% ozone yield. Following the generation of ozone, the gas must be transferred to the water using a gas contact reactor, usually with 5-20 min hydraulic retention time [5,7,16].

When ClO_2 is used for oxidation of water with low NOM (natural organic matter), most of the ClO_2 is reduced to chlorite by reactions with the organic matter. Chlorate is also formed as a by-product, but at a much lower concentration than chlorite [17, 18,19]. According to Korn [18] and Lee [19], the formation of chlorite and chlorate accounts for about 70% and 10%, respectively, of the chlorine dioxide applied. In drinking water with low NOM, chlorite reacts slowly with organic matter and is reduced to chloride, while in wastewater, significantly more NOM is available to reduce the chlorite. Toxicity derived from chlorite residuals after treatment may be problematic depending on the concentration and degradation rate [20]. ClO_2 differs from chlorine in that it produces very little chloro-organic by-products [11,15,21].

The formation of undesirable by-products can be controlled by minimizing the dose of ClO_2 and applying post-treatment using, for example, ferrous iron (Fe^{2+}) or sulfite (SO_3^{2-}), which reduces ClO_2 and chlorite residuals to chloride [22,23]. The removal of ClO_2 and chlorite residuals allows higher levels of ClO_2 to be used for treatment providing effective micropollutant removal.

In this study, the removal of 56 different APIs in biologically treated wastewater was investigated in both low- and high-COD effluents using different doses of chlorine dioxide. The APIs were chosen to represent different classes of pharmaceuticals commonly sold and used in Sweden, which will most likely end up in WWTP effluents due to their low sorption to sludge [24]. The effectiveness of the treatment was evaluated by monitoring the oxidant consumption and the amount of APIs oxidized. Oxidation by-products were not evaluated in this study as the aim was to determine the most suitable oxidant dose and identify which APIs can be removed. Once the relevant dose has been determined, attention can be turned towards investigating the ClO_2 by-products.

2. Materials and methods

2.1. Chemicals

All pharmaceutical reference standards were purchased as solids of analytical grade (>98%) from different suppliers. All APIs investigated are listed in Supplementary Information Table S1. Methanol and acetonitrile were of LC/MS grade (Merck, Darmstadt, Germany). Ultrapure water was prepared from deionized water using a Milli-Q Gradient system (Millipore, Billerica, MA), equipped with a UV radiation source. A stock solution of APIs was prepared in methanol at concentration of about 100 mg/L. Solutions for spiking and analysis were prepared by precise dilution of the stock solution. Chlorine dioxide was synthesized by adding equal volumes (25 mL each) of 9% HCl (Merck, Darmstadt, Germany) and 7.5% $NaClO_2$ (Sigma Aldrich, Steinheim, Germany) to 400 mL deionized water. The solution was allowed to react in the dark for at least 10 hours and then diluted to 1000 mL with water. This resulted in an approximately 1 g/L ClO_2 stock solution.

2.2. Analytical methods

The concentration of residual ClO_2 was quantified by reaction with DPD (N,N-diethyl-p-phenylenediamine) using an Allcon spectrophotometer (Alldos GmbH,

Germany) with a built-in calibration line for ClO_2. The analysis of ClO_2 with DPD was performed according to the manufacturer's instructions.

For the analysis of the APIs, samples of 100 mL treated effluent were filtered using a 0.45 μm membrane filter (Millipore, Ireland) then acidified to pH 3 using sulfuric acid. Five ng of ^{13}C- and ^{2}H-labelled APIs was added as internal standards, to each sample (see Supplementary Table 1 for the complete list) before solid-phase extraction using Oasis HLB columns (200 mg, Waters). LC/MS/MS analysis of the extracts was carried out using a triple-stage quadrupole mass spectrometer (MS/MS TSQ Quantum Ultra EMR) coupled to an Accela LC pump (both from Thermo Fisher Scientific, San Jose, CA, USA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland) with a Hypersil GOLD aQ^{TM} column (50 mm x 2.1 mm ID x 5 μm particles). Both heated electrospray and atmospheric pressure photoionization were used in positive and negative ion modes for the ionization of target compounds. Two MS/MS transitions were measured for each API. Samples were quantified using isotope dilution or internal standard methods. Six points calibration curve corresponding to concentration ranges 10 to 2500 ng/L were measured before, in the middle and at the end of sample analysis sequence to monitor response factor stability. Recoveries and the relative standard deviation of triplicate analyses of effluent from the Sjölunda WWTP spiked at 1μg/L are given in Supplementary Information Table S2. Maximum difference between results at quantification and qualification mass transition was set to 30% as criterion for positive identification of the analyte. The same method is used by Hörsing et al. [24] and Grabic et al. (unpublished results) [25].

2.3. Experimental setup

2.3.1. Wastewater effluents

Wastewater effluents were collected after secondary treatment from two WWTPs in southern Sweden. Effluent 1 was collected from Källby WWTP after the activated sludge system which is operated with extended nitrogen removal.

Effluent 2 was obtained from Sjölunda WWTP after a high loaded activated sludge process before nitrogen removal. This wastewater is typical of that in many Swedish WWTPs which are operated without nitrogen removal due to their location in the northern part of the country where the climate is colder. Sjölunda also employs full nitrogen removal but using a biofilm system after a highly loaded activated sludge

plant. Nitrification is achieved in trickling filters and denitrification in moving bed biofilm reactors with the addition of external carbon.

Table 1 gives the characteristics of the effluents. The effluents were analyzed using standard Swedish methods for total suspended solids (SS-EN 872:2005), total P (SS-EN ISO 6878:2005) and total N (SS-EN ISO 11905-1), while COD was determined with the Dr. Lange LCK 114 kit. The effluents were classified as low COD (Effluent 1) or high COD effluent (Effluent 2) based on their COD levels.

Table 1
Effluent characteristics

	pH	COD (mg/L)	TSS (mg/L)	Total P (mg/L)	Total N (mg/L)
Effluent 1 (Källby)	6.8	35	5	0.26	7.5
Effluent 2 (Sjölunda)	7.2	55	8	0.28	8.0

2.3.2. Oxidation experiments

Effluent samples of 150 mL each were prepared in Schott Duran® bottles and spiked with mixed APIs to a final concentration of approx. 1 μg/L. ClO_2 was added to duplicate samples at concentrations ranging from 0-20 mg/L. All samples were stored in the dark and allowed to react overnight (approx. 18 h) at room temperature, after which the pH and oxidant concentration in the samples were measured. Residual oxidants were removed by the addition of 50 mg/L sodium sulfite.

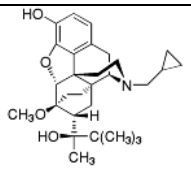
3. Results and discussion

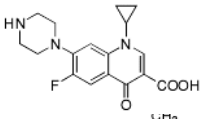
Table 2 lists the APIs investigated, including information on the class of drug, arranged according to the ease with which they were oxidized by ClO_2 (based on Effluent 1).

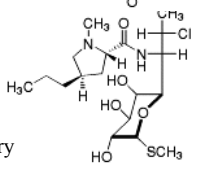
No further pH adjustments were made during the entire experiment. The pH of the samples did not change significantly after treatment, even with the highest oxidant dose of 20 mg/L, where the sample remained slightly acidic (~pH 6.2-6.5). This slight decrease in pH is expected since the stock solutions of ClO_2 contain some residual HCl from the synthesis.

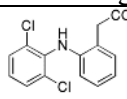
Table 2
Name and chemical structure of the APIs investigated (www.fass.se). The therapeutic class, and in the case of the easily and moderately oxidizable APIs the reactive functional group are given in brackets.

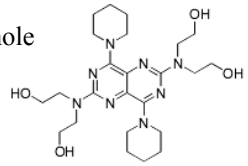
Easily oxidized (0.5-1.25 mg/l ClO_2)

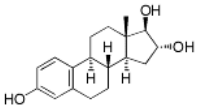
Buprenorphine (narcotic analgesic; phenol)


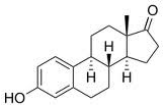
Ciprofloxacin (antibiotic; tertiary amine)


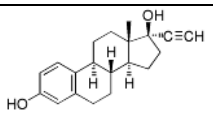
Clindamycine (antibiotics; tertiary amine)


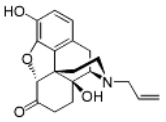
Diclofenac (antiphlogistic; aniline)


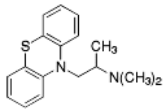
Dipyridamole (antiplatelet; tertiary amine)


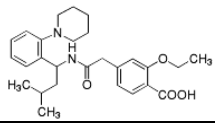
Estriol (hormone; phenol)


Estrone (hormone; phenol)


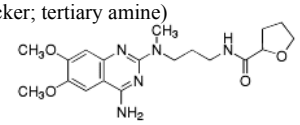
Ethinyl estradiol (hormone; phenol)


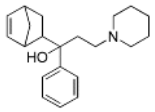
Naloxone (narcotic antagonist; phenol)


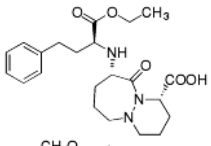
Promethazine (antihistamine; tertiary amine)


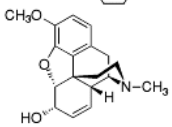
Repaglinide (antidiabetic; tertiary amine)


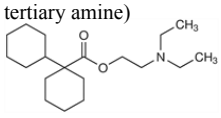
Moderately oxidized (2.5-5 mg/L ClO_2)

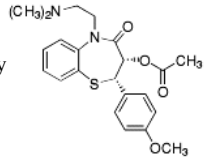
Alfuzosin (α-blocker; tertiary amine)


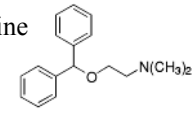
Biperiden (antiparkinson; tertiary amine)


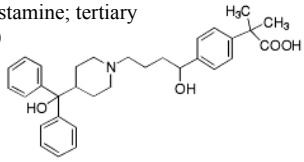
Cilazapril (ACE inhibitor; tertiary amine)


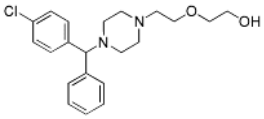
Codeine (narcotic analgesic; tertiary amine)


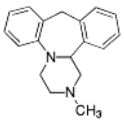
Dicyloverin (anticholinergic; tertiary amine)


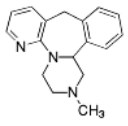
Diltiazem (calcium antagonist; tertiary amine)


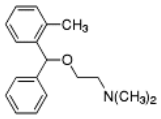
Diphenhydramine (anxiolytic; tertiary amine)


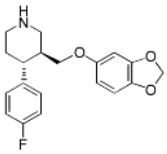
Fexofenadine (antihistamine; tertiary amine)


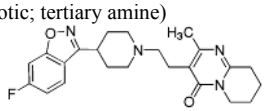
Hydroxyzine (antihistamine; tertiary amine)


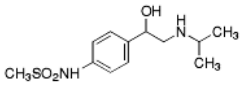
Mianserin (antidepressant; tertiary amine)


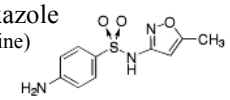
Mirtazapine (antidepressant; tertiary amine)


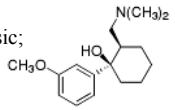
Orphenadrine (anticholinergic; tertiary amine)


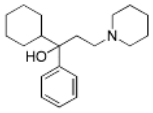
Paroxetine (antidepressant; secondary amine, cyclic)


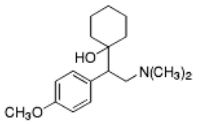
Risperidone (antipsychotic; tertiary amine)


Sotalol (β-locker; sulfonamide)


Sulfamethoxazole (antibiotic; aniline)


Tramadol (narcotic analgesic; tertiary amine)


Trihexyphenidyl (antiparkinson; tertiary amine)


Venlafaxine (antidepressant; tertiary amine)


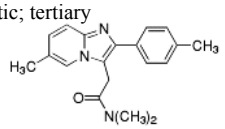
Zolpidem (sedative hypnotic; tertiary amine)


Table 2. Continued.

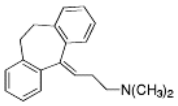
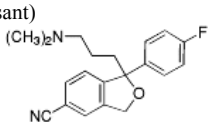
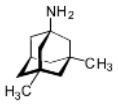
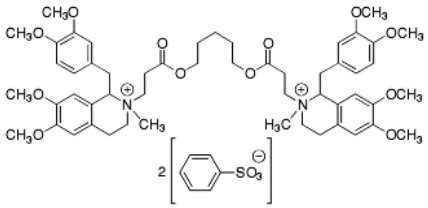
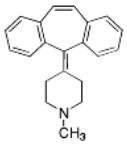
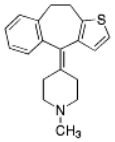
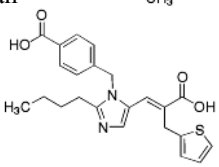
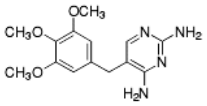
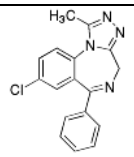
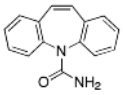
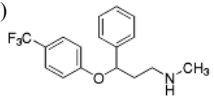
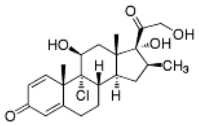
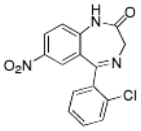
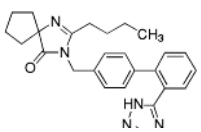
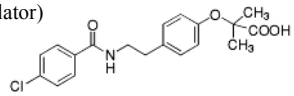
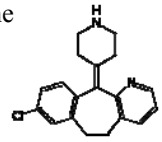
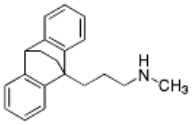
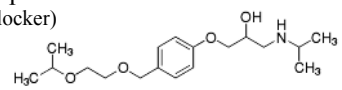
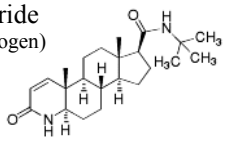
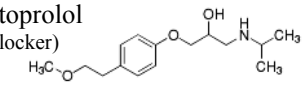
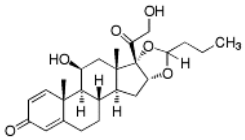
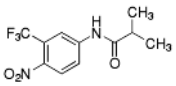
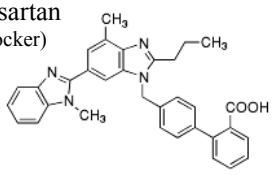
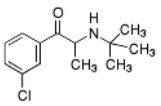
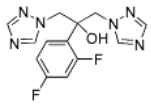
Poorly oxidized (8-20 mg/L ClO_2)		
Amitriptyline (antidepressant) 	Citalopram (antidepressant) 	Memantine (antidementia) 
Atracurium (neuromuscular blocker) 	Cyproheptadine (antihistamine) 	Pizotifen (serotonin antagonist) 
	Eprosartan (AR blocker) 	Trimethoprim (antibiotic) 
Non-oxidizable		
Alprazolam (anxiolytic) 	Carbamazepine (antiepileptic) 	Fluoxetine (antidepressant) 
Beclomethasone (synthetic steroid) 	Clonazepam (antiparkinson) 	Irbesartan (AR blocker) 
Bezafibrate (lipid regulator) 	Desloratidine (antihistamine) 	Maprotiline (antidepressant) 
Bisoprolol (β-blocker) 	Finasteride (antiandrogen) 	Metoprolol (β-blocker) 
Budesonide (synthetic steroid) 	Flutamide (antiandrogen) 	Telmisartan (AR blocker) 
Bupropion (antidepressant) 	Fluconazole (antifungal) 	

Figure 1 shows the residual concentration of ClO_2 in the two effluents spiked with APIs as a function of the initial ClO_2 dose. It can be seen that the high COD

effluent consumed more oxidant than the low COD effluent, especially when the dose was 8 mg/L ClO_2 and above.

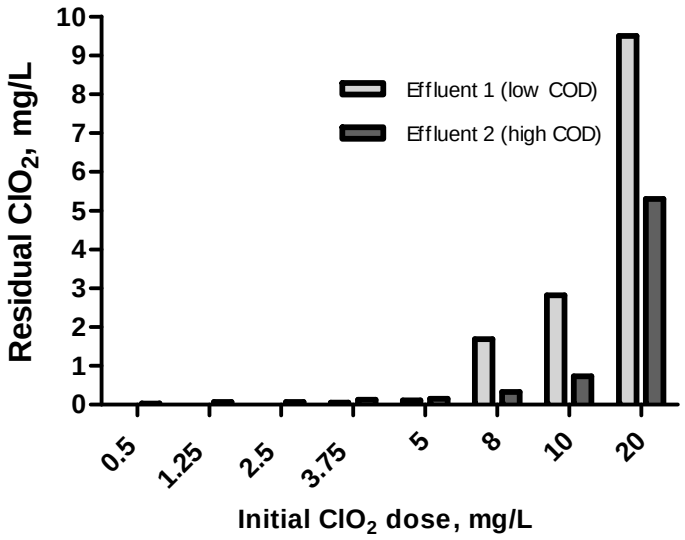


Figure 1. Residual concentration of ClO2 in the 2 effluents after treatment with different doses of the oxidant.

Table 3 gives the number of APIs that can be effectively oxidized (i.e. by more than 90%) at each ClO_2 dose in both effluents. It can be seen that a dose of 8 mg/L ClO_2 to Effluent 1 was able to oxidize 38 of 56 APIs, and that only 1 more API was oxidized when the dose was increased to 20 mg/L. In Effluent 2, 33 APIs were oxidized with a dose of 8 mg/L ClO_2, and increasing the ClO_2 dose to 20 mg/L oxidized further 4 APIs. The remaining APIs (about one third) could not be degraded effectively (at least 90%) with a dose of 20 mg/L ClO_2.

Only few APIs were oxidized by more than 90% at the lowest dose of ClO_2 (0.5 mg/L), while high oxidative degradation was observed with higher doses (8-20 mg/L). The degree to which each API was oxidized at different ClO_2 doses is shown in Figure 2A and 2B for Effluents 1 and 2, respectively. The vertical lines divide the APIs into easily, moderately, poorly (based on the ClO_2 dose required to achieve 90-100% degradation) and non-oxidizable APIs (less than 90% degradation with 20 mg/L ClO_2).

As shown for Effluent 1 (Figure 2A and Table 2), 11 of the APIs from 8 different therapeutic classes could be oxidized by more than 90% with 0.5-1.25 mg/L ClO_2. These include all 3 hormones, 2 antibiotics, 1 antihistamine, and 1 narcotic analgesic,

as well as the antiplatelet, antidiabetic, antiphlogistic and narcotic antagonist compounds. The common reactive and electron-rich functional groups in these APIs are aniline in diclofenac, phenol in hormones, buprenorphine, and naloxone, and tertiary amines in promethazine, clindamycine, dipyridamole, repaglinide and ciprofloxacin. The high reactivity of ClO_2 with aniline, phenolic and tertiary amine functional groups has been reported in a number of studies [6,10,26]. The reactivity of ClO_2 with the piperazine ring of the antibiotic ciprofloxacin has also been reported by Wang et al. [13]. Similarly, Navalon et al. [12] also showed high reactivity of ciprofloxacin with ClO_2 in both surface water and wastewater effluent.

Table 3
The number of APIs tested (of a total of 56) that could be effectively oxidized (at least 90%) at each ClO_2 dose

	No. of APIs oxidized by > 90%	
ClO_2 dose, mg/l	(Effluent 1)	(Effluent 2)
0.5	4	0
1.25	11	4
2.5	15	8
3.75	24	12
5	31	18
8	38	33
10	38	36
20	39	37

APIs requiring doses of 2.5-5 mg/L ClO_2 for oxidation are considered to be moderately oxidizable (Table 2). Most of the APIs from 13 of the different therapeutic classes belong to this category including 4 antidepressants, 2 antihistamines, 2 antiparkinson drugs, 2 narcotic analgesics, 2 anticholinergics, 1 antibiotic, 1 beta blocker, 1 sedative-hypnotic, 1 anxiolytic, and the representative compound from different classes, namely angiotensin converting enzyme (ACE) inhibitor, alpha blocker, antipsychotic and calcium antagonist. The most common functional group in this category of moderately oxidizable APIs is the tertiary amino group, which is also found in the structures of easily oxidizable APIs. However, despite belonging to the same therapeutic class, the behavior of the APIs differed significantly, depending largely on the reactivity of electron-rich functional groups. The removal of pharmaceuticals at fairly low oxidant doses (1.25-3.75 mg/L ClO_2) has also been

observed in previous studies on surface and drinking water [10] and in wastewater effluents [6,11].

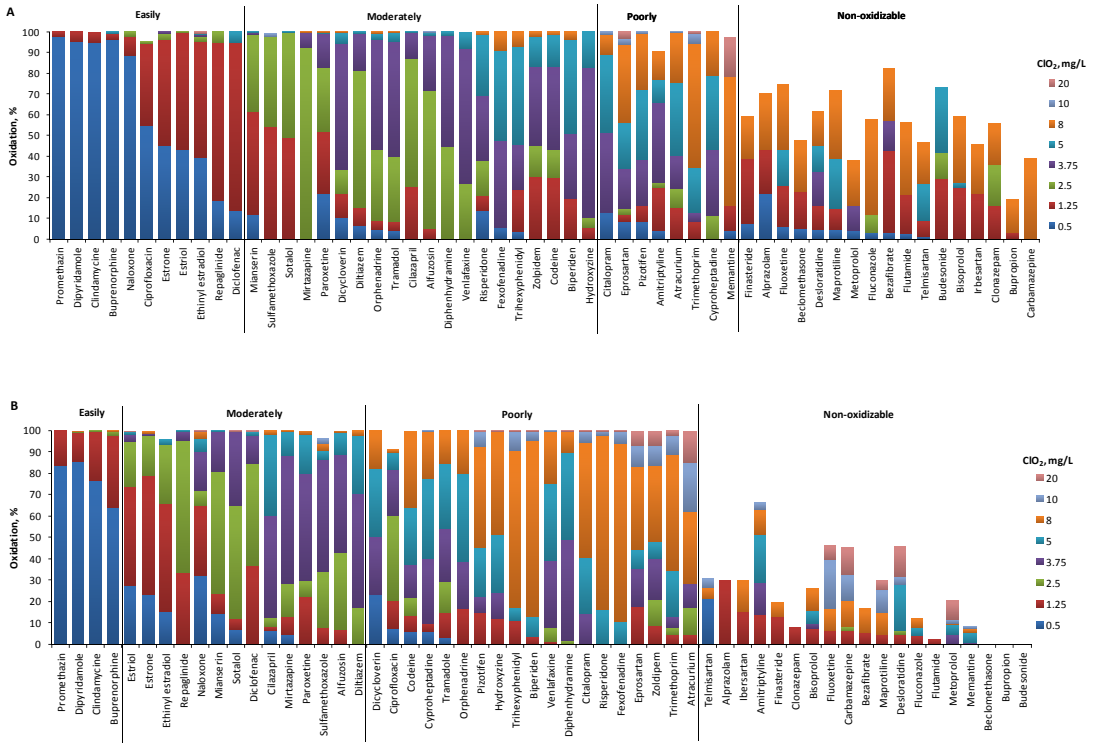


Figure 2. Fraction of APIs oxidized in Effluent 1 (A) and Effluent 2 (B) at different ClO_2 doses. The vertical lines divide the APIs into groups according to their ease of oxidation.

The resistance of poorly and non-oxidizable APIs to oxidation by ClO_2 could be attributed to the presence of the electron-withdrawing functional groups such as the chloro (in clonazepam, bupropion, desloratidine, alprazolam, bezafibrate, and beclomethasone), fluoro (in citalopram, flutamide, fluoxetin, fluconazole), nitro (in flutamide and clonazepam), olefin or C=C double bonds (in eprosartan and amitriptyline), amide carbonyl (in bezafibrate and finasteride) and keto group (in bupropion, beclomethasone and budesonide) [7,26,27,28,29]. The secondary amine-containing beta blockers, metoprolol and bisoprolol are also considered less susceptible to ClO_2 oxidation. Lee and von Gunten [6] reported the poor transformation of the beta blocker atenolol which has a secondary amine functional group. However, the oxidizability of the beta blocker sotalol can be explained by the presence of the ClO_2 reactive sulfonamide functional group in its structure. The same

degree of API oxidation can be achieved in the high COD effluent (2) as in the low COD effluent (1), but higher ClO_2 doses are required. This is due to consumption of the ClO_2 competitively with the APIs by other organic components in the wastewater [6]. In addition, the presence of inorganic components in the wastewater also consumes some of the oxidant and this could affect the removal of the target micropollutants [6].

The results of this study showed that about 20 APIs cannot be oxidized effectively, even at the highest dose investigated (20 mg/L ClO_2), suggesting low reactivity between these APIs and ClO_2. In Effluent 1, 13 of these APIs (alprazolam, finasteride, fluoxetine, beclomethasone, desloratadine, maprotiline, fluconazole, bezafibrate, flutamide, telmisartan, budesonide, bisoprolol, and clonazepam) were oxidized by 50-80%, while the remaining 4 APIs metoprolol, irbesartan, bupropion, and carbamazepine were degraded less (20-40%). On the other hand, in Effluent 2, most of these APIs were oxidized by less than 50%, while 3 APIs (the synthetic steroids beclomethasone and budesonide, and the antidepressant bupropion) did not show any degradation at all. Bezafibrate and carbamazepine have been shown in previous investigations to be recalcitrant to ClO_2 oxidation during water and wastewater treatment [10,6,28]. As mentioned above, the presence of electron-withdrawing functional groups results in low reactivity of some APIs to ClO_2 oxidation, and thus a much higher dose of ClO_2 would be needed for oxidation.

APIs such as diclofenac, sulfamethoxazole and estrogens have been found to be oxidized by more than 90% during ozonation of municipal wastewater effluents at O_3 doses of $\geq$ 2 mg/L, while a much higher O_3 dose was required for the effective removal of bezafibrate [30]. Ternes et al. [7] also found significant removal (> 90%) of sulfamethoxazole, diclofenac, carbamazepine, and sotalol during treatment of municipal sewage effluent with 5 mg/L O_3, while a higher O_3 dose of 10-15 mg/L was required to effectively remove the beta blocker metoprolol, which also exhibits low reactivity to ClO_2. In the present study, ClO_2 was able to oxidize several APIs effectively at doses comparable to those of ozone. The reactivity of carbamazepine was very different since it could be removed by low ozone doses, while it is almost completely resistant to ClO_2.

The oxidation of APIs by ClO_2 is comparable to oxidation by molecular ozone as both are selective oxidants and are capable of transforming organic micropollutants

based on the reactivity of the structure and the characteristics of the water matrix. These chemical oxidants react with electron-rich functional groups such as phenolic and amino groups, which can be found in the structures of most of the APIs investigated [6,10,31,32,33]. However, the reaction between ClO_2 and some APIs was much slower than ozonation, even with the same reactive functional group. Therefore, the usefulness of ClO_2 end-of-pipe treatment of WWTP effluents will depend on whether the micropollutants deemed to be critical for the receiving water are sensitive to ClO_2. Running costs must also be considered since ClO_2 is slightly more expensive to produce than ozone, while it is far simpler and less expensive to build both the generator and reaction chamber for ClO_2 treatment. The treatment perspective then is mainly to use ClO_2-treatment for small scale WWTP (< 2,000 person equivalent) effluents or where treatment is required only for a limited time.

Two of the APIs investigated here may be of considerable concern regarding the discharge of wastewater effluents into surface water. Both ethinyl estradiol, a pharmaceutical with a high endocrine-disrupting ability [34], and diclofenac, identified as a contaminant that causes direct toxic effects in the environment [35,36], were found to be very sensitive to ClO_2 oxidation. However, if other less reactive APIs, e.g. bezafibrate or carbamazepine, were found to be of concern regarding aquatic life in the receiving water body of the WWTP effluent, ClO_2 treatment would not be a suitable treatment option.

4. Conclusions

The results of this study show that ClO_2 can be used to treat wastewater effluents to oxidize various APIs belonging to different therapeutic classes. However, there was considerable variation in the reactivity of the investigated APIs to ClO_2. The degree of oxidation was found to be dependent on the type of wastewater; API removal is better from the low COD wastewater from the plant with extended nitrogen removal, than the one without (high COD wastewater), at the same oxidant dose. In addition, the reactivity of the APIs depends on the reactive functional group present. APIs with electron-withdrawing functional groups appear to be more resistant to ClO_2 oxidation.

ClO_2 oxidation by-products and toxicity must be investigated before this method can be considered for application in wastewater treatment. The use of ClO_2 oxidation

for the removal of pharmaceuticals may be beneficial in small wastewater treatment plants where ozonation could be too expensive and complicated.

Acknowledgements

The authors would like to thank the Swedish Foundation for Strategic Environmental Research through the MistraPharma programme for the full financial support of this study.

References

[1] K. Kimura, H. Hara, Y. Watanabe, Removal of pharmaceutical compounds by submerged membrane bioreactors (MBRs), Desalination 178 (2005) 135-140.
[2] N.M. Vieno, T. Tuhkanen, L. Kronberg, Seasonal variation in the occurrence of pharmaceuticals in effluents from a sewage treatment plant and in the recipient water, Environ. Sci. Technol. 39 (2005) 8220-8226.
[3] K. Fent, A.A. Weston, D. Caminada, Ecotoxicology of human pharmaceuticals, Aquat. Toxicol. 76 (2006) 122-159.
[4] S.A. Snyder, Occurrence, treatment, and toxicological relevance of EDCs and pharmaceuticals in water, Ozone-Sci. Eng. 30 (2008) 65-69.
[5] K.M.S. Hansen, H.R. Andersen, A. Ledin, Ozonation of estrogenic chemicals in biologically treated sewage, Water Sci. Technol. 62 (2010) 649-657.
[6] Y. Lee, U. von Gunten, Oxidative transformation of micropollutants during municipal wastewater treatment: comparison of kinetic aspects of selective (chlorine, chlorine dioxide, ferrate^{VI}, and ozone) and non-selective oxidants (hydroxyl radical), Water Res. 44 (2010) 555-566.
[7] T.A. Ternes, J. Stuber, N. Herrmann, D. McDowell, A. Ried, M. Kampmann, B. Teiser, Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater?, Water Res. 37 (2003)1976-1982.
[8] F.J. Benitez, J.L. Acero, F.J. Real, G. Roldan, F. Casas, Comparison of different chemical oxidation treatments for the removal of selected pharmaceuticals in water matrices, Chem. Eng. J. 168 (2011) 1149-1156.
[9] T.A Ternes, Occurrence of drugs in German sewage treatment plants and rivers, Water Res. 32 (1998) 3245-3260.
[10] M.M. Huber, S. Korhonen, T.A. Ternes, U. von Gunten, Oxidation of pharmaceuticals during water treatment with chlorine dioxide, Water Res. 39 (2005) 3607-3617.
[11] H.R. Andersen, Use of ClO_2 for removal of estrogenic substances in wastewater, Patent WO2010/023311, 2010 Mar 4.
[12] S. Navalon, M. Alvaro, H. Garcia, Reaction of chlorine dioxide with emergent water pollutants: product study of the reaction of three β-lactam antibiotics with ClO_2, Water Res. 42 (2008) 1935-1942.
[13] P. Wang, Y. He, C. Huang, Oxidation of fluoroquinolone antibiotics and structurally related amines by chlorine dioxide: reaction kinetics, product and pathway evaluation, Water Res. 44 (2010) 5989-5998.

[14] G. Hey, A. Ledin, J. la Cour Jansen, H.R. Andersen, Removal of pharmaceuticals in biologically treated wastewater by chlorine dioxide or peracetic acid, Environ. Technol. (2011) Online preprint. doi:10.1080/09593330.2011.606282.
[15] H.R. Andersen, M. Lundsbye, H.W. Vedel, E. Eriksson, A. Ledin, Estrogenic personal care products in a greywater reuse system, Water Sci. Technol. 56 (2007) 45–49.
[16] A. Ried, J. Mielcke, A. Wieland, The potential use of ozone in municipal wastewater, Ozone-Sci. Eng. 31 (2009) 415-421.
[17] V. Csordas, B. Bubnis, I. Fabian, G. Gordon, Kinetics and mechanism of catalytic decomposition and oxidation of chlorine dioxide by the hypochlorite ion, Inorg. Chem. 40 (8) (2001) 1833-1836.
[18] C. Korn, R.C. Andrews, M.D. Escobar, Development of chlorine dioxide-related by-product models for drinking water treatment, Water Res. 36 (2002) 330-342.
[19] Y. Lee, H. Kim, U. Lee, Formation of chlorite and chlorate from chlorine dioxide with Han river water, Korean J. Chem. Eng. 21 (3) (2004) 647-653.
[20] D. Gates, G. Zigilio, K. Ozekin, State of the Science of Chlorine Dioxide in Drinking Water, American Water Research Foundation ISBN: 9781605730509, 2011.
[21] M.M. Huber, Elimination of pharmaceuticals during oxidative treatment of drinking water and wastewater: application of ozone and chlorine dioxide (dissertation). Swiss Federal Institute of Technology Zurich, 2004.
[22] A. Katz and N. Narkis, Removal of chlorine dioxide disinfection by-products by ferrous salts, Water Res. 35 (1) (2001) 101-108.
[23] M.H. Griese, K. Hauser, M. Berkemeier, G. Gordon, Using reducing agents to eliminate chlorine dioxide and chlorite ion residuals in drinking water, J. Am. Water Works Ass. 83 (5) (1991) 56-61.
[24] M. Hörsing, A. Ledin, R. Grabic, J. Fick, M. Tysklind, J. La Cour Jansen, H.R. Andersen, Determination of sorption of seventy-five pharmaceuticals in sewage sludge, Water Res. 45 (2011) 4470-4482.
[25] R. Grabic, J. Fick, R.H. Lindberg, G. Fedorova, M. Tysklind, Multi-residue method for determination of trace levels of 100 pharmaceuticals in environmental samples using liquid chromatography coupled to triple quadrupole mass spectrometry, (unpublished results).
[26] J. Hoigné, H. Bader, Kinetics of reaction of chlorine dioxide (OClO) in water –i. rate constants for inorganic and organic compounds, Water Res. 28 (1) (1994) 45-55.
[27] B. Razavi, W. Song, W.J. Cooper, J. Greaves, J. Jeong, Free-Radical-Induced Oxidative and Reductive Degradation of Fibrate Pharmaceuticals: Kinetic Studies and Degradation Mechanisms, J. Phys. Chem. A 113 (2009) 1287-1294.
[28] T. Kosjek, H.R. Andersen, B. Kompare, A. Ledin, E. Heath, Fate of carbamazepine during water treatment, Environ. Sci. Technol. 43 (2009) 6256-6261.
[29] A.B.C. Alvares, C. Diaper, S.A. Parsons, Partial oxidation by ozone to remove recalcitrance from wastewaters: a review, Environ. Technol. 22 (2010) 409-427.
[30] M.M. Huber, A Göbel., A. Joss, N. Hermann, D. Löffler, C.S. Mcardell, A. Ried, H. Siegrist, T.A. Ternes, U. von Gunten, Oxidation of pharmaceuticals during ozonation of municipal wastewater effluents: a pilot study. Environ. Sci. Technol. 39 (2005) 4290-4299.

[31] M.O. Buffle, U. von Gunten, Phenols and amine induced $HO^{\bullet}$ generation during the initial phase of natural water ozonation, Environ. Sci. Technol. 40 (2006) 3057-3063.
[32] V.K. Sharma, Oxidative transformation of environmental pharmaceuticals by Cl_2, ClO_2, O_3 and Fe (VI): kinetics assessment, Chemosphere 73 (2008) 1379-1386.
[33] D. Vogna, R. Marotta, A. Napolitano, R. Andreozzi, M. d'Ischia, Advanced oxidation of the pharmaceutical drug diclofenac with UV/H_2O_2 and ozone, Water Res. 38 (2004) 414-422.
[34] A.O. Ifelebuegu, The fate and behaviour of selective endocrine disrupting chemicals in full scale wastewater and sludge treatment unit processes, Int. J. Environ. Sci. Technol. 8 (2011) 245-254.
[35] J.L. Oaks, M. Gilbert, M.Z. Virani, R.T. Watson, C.U. Meteyer, B.A. Rideout, H.L. Shivaprasad, S. Ahmed, M.J.I. Chaudry, M. Arshad, S. Mahmood, A. Ali, A.A. Khan, Diclofenac residues as the cause of vulture population decline in Pakistan, Nature 427 (2004) 630-633.
[36] V. Naidoo, G.E. Swan, Diclofenac toxicity in Gyps vulture is associated with decreased uric acid excretion and not renal portal vasoconstriction, Comp. Biochem. Phys. C. 149 (2009) 269-274.

Web reference

[1] http://www.fass.se/LIF/home/index.jsp (accessed 22.07.11).

Supplementary Materials

Oxidation of pharmaceuticals by chlorine dioxide in biologically treated wastewater

G. Hey[a,*], R. Grabic[b], A. Ledin[a,c], J. la Cour Jansen[a], H.R. Andersen[c]
[a] Water and Environmental Engineering, Department of Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden

[b] Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden

[c] Department of Environmental Engineering, Technical University of Denmark, Miljøvej, Building 113, DK-2800 Kongens Lyngby, Denmark

*Corresponding author: Gerly Hey, Phone: +46 46 222 8998; fax: +46 46 222 4526

Email: gerly.moradas@chemeng.lth.se

Table S1
List of suppliers for APIs and the corresponding internal standards used for quantification.

APIs	Supplier	Internal standards	Supplier
Alfuzosin	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Alprazolam	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Amitryptiline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Atracurium	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Beclomethasone	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_5$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Bezafibrate	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_5$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Biperiden	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Bisoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Budesonide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_5$ - Fluoxetine	Cambridge Isotope Laboratories (Andover, MA, USA)
Buprenorphine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Bupropion	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Carbamazepine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Cilazapril	LGC Standards (Middlesex, UK)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Ciprofloxacin	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3{}^{15}N$ - Ciprofloxacin	Cambridge Isotope Laboratories (Andover, MA, USA)
Citalopram	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Clindamycine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Clonazepam	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Codeine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Cyproheptadine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)

Desloratidine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{4}$ - Risperidone	Sigma-Aldrich (Steinheim, Germany)
Diclofenac	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Dicycloverin	LGC Standards (Middlesex, UK)	$^{2}H_{5}$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Diltiazem	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diphenhydramine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Dipyridamole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Eprosartan	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Estriol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{2}$. Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Estrone	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{2}$. Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Ethinyl estradiol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{2}$. Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Fexofenadine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Finasteride	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{5}$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Fluconazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{3}$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Fluoxetine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{5}$ - Fluoxetine	Cambridge Isotope Laboratories (Andover, MA, USA)
Flutamide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Hydroxyzine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Irbesartan	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Maprotiline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Memantine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Metoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Mianserin	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Mirtazapine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Naloxone	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Orphenadrine	LGC Standards (Middlesex, UK)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Paroxetine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Pizotifen	LGC Standards (Middlesex, UK)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Promethazine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Repaglinide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Risperidone	LGC Standards (Middlesex, UK)	$^{2}H_{4}$ - Risperidone	Sigma-Aldrich (Steinheim, Germany)
Sotalol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Sulfamethoxazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{6}$ - Sulfamethoxazole	Cambridge Isotope Laboratories (Andover, MA, USA)
Telmisartan	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Tramadol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Trihexyphenidyl	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Trimethoprim	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{3}$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Venlafaxine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Zolpidem	LGC Standards (Middlesex, UK)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)

Table S2
Ionization mode, recoveries and relative standard deviation (RSD) of the APIs

API	Ionization mode	Recovery (average of triplicate)	RSD
		%	%
Alfuzosin	HESI	111	6.2
Alprazolam	HESI	67.8	2.8
Amitryptiline	HESI	83.3	7.5
Atracurium	HESI	85.8	7.2
Beclomethasone	HESI	25.2	12.9
Bezafibrate	HESI	126	1.1
Biperiden	HESI	106	8.4
Bisoprolol	HESI	83.1	5.1
Budesonide	HESI	111	9.5
Buprenorphine	HESI	88.6	5.3
Bupropion	HESI	96.3	4.7
Carbamazepine	HESI	101	15.1
Cilazapril	HESI	143	5.9
Ciprofloxacin	HESI	86.3	4.1
Citalopram	HESI	83.6	8.5
Clindamycine	HESI	76.7	9.4
Clonazepam	HESI	67.6	5.8
Codeine	HESI	86.7	24.0
Cyproheptadine	HESI	80.0	2.4
Desloratidine	HESI	57.1	4.0
Diclofenac	HESI	42.1	4.4
Dicycloverin	HESI	84.1	7.7
Diltiazem	HESI	107	3.8
Diphenhydramine	HESI	99.0	15.1
Dipyridamole	HESI	72.0	7.6
Eprosartan	HESI	62.3	4.3
Estriol	APCI/APPI	129	24.7
Estrone	APCI/APPI	134	19.9
Ethinyl estradiol	APCI/APPI	85.7	4.1
Fexofenadine	HESI	81.1	7.1
Finasteride	HESI	80.0	5.1
Fluconazole	HESI	89.8	12.9
Fluoxetine	HESI	97.0	11.4
Flutamide	HESI	91.8	3.9
Hydroxyzine	HESI	94.5	14.2
Irbesartan	HESI	109	2.6
Maprotiline	HESI	84.1	7.4
Memantine	HESI	85.7	7.7
Metoprolol	HESI	82.9	1.3
Mianserin	HESI	81.0	12.5
Mirtazapine	HESI	90.3	17.3
Naloxone	HESI	75.8	30.2
Orphenadrine	HESI	94.7	11.2
Paroxetine	HESI	62.7	5.5
Pizotifen	HESI	90.8	5.3
Promethazine	HESI	108	6.7
Repaglinide	HESI	93.4	8.6
Risperidone	HESI	101	2.4

Sotalol	HESI	125	14.7
Sulfamethoxazole	HESI	97.3	4.3
Telmisartan	HESI	106	15.2
Tramadol	HESI	129	6.3
Trihexyphenidyl	HESI	124	12.2
Trimethoprim	HESI	109	10.7
Venlafaxine	HESI	96.2	7.8
Zolpidem	HESI	94.3	4,4
Median		91	7.3
Min		25	1.1
Max		143	30

Note:
Recovery experiment at 1000 ng/L (n=3). 3 APIs has recovery of < 60%; 1 API has recovery of > 130%