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Hospital Wastewater Treatment with Pilot-Scale Pulsed Corona Discharge for Removal of Pharmaceutical Residues

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Abstract In recent years, accumulation of pharmaceutical compounds in the environment has been an issue of growing concern. Conventional wastewater treatment has limited effectiveness with many pharmaceuticals at concentrations of ppb or ppt scale. An intuitive solution would be to treat the pharmaceuticals-contaminated wastewaters at the source sites before dilution in sewer networks. Health institutions with concentrated drug consumption provide logical point

sources for pharmaceuticals entering the sewage. This paper describes the pilot-scale removal of a wide range of pharmaceuticals from real wastewaters via gas-phase pulsed corona discharge oxidation. The process was studied for raw sewage from a public hospital and for biologically treated wastewater of a health-care institute. The non-selective oxidation of the observed pharmaceuticals (32 compounds) was effective at reasonable energy cost: 87-% reduction in residual pharmaceuticals (excluding biodegradable caffeine) from raw sewage was attained with 1 kWh m⁻³ from the raw sewage and 100% removal was achieved for biologically treated wastewater at only 0.5 kWh m⁻³. The impact for affected aquatic environments upon the present solution would be a dramatically reduced load of pharmaceutical accumulation.

Keywords Non-thermal plasma, Micropollutant, Drug, Hydroxyl radical, Ozone

Highlights

- A plasma pilot system is used for drugs abatement from point source wastewaters
- An extensive range of 57 aqueous pharmaceuticals was monitored in plasma oxidation
- Substantial reduction of residual medicines was achieved at feasible energy cost

1. Introduction

Medicinal compounds pose a threat to aquatic environments due to their biological activity. The issue has received wide scientific and public media attention in recent years [1,2]. A structural challenge in addressing this problem comes not only from the persistence commonly exhibited by such substances, but also from the very low concentrations at which they occur. These two factors make the removal of pharmaceutical residues in conventional wastewater treatment plants essentially insufficient with rare exceptions, e.g. ibuprofen, a common non-steroidal anti-inflammatory drug, exhibiting significant biological transformation [3]. In fact, biological water treatment process may even increase the amount of certain pharmaceuticals due to enzymatic reformation of metabolites, reproducing the original parent compounds, which has been observed for example for the anti-epileptic carbamazepine [4] and certain hormones.

Natural and synthetic hormones present in the sanitary fraction of wastewaters mainly enter wastewater treatment plants (WWTPs) in largely non-estrogenic form, excreted primarily as a variety of inactive glucuronide or sulfonide conjugates. During the sewage process, however, these inactive compounds are readily transformed into potentially more harmful ones [5]. This transformation seemingly happens due to the large amounts of β -glucuronidase enzyme produced by the fecal bacteria *Escherichia coli* [6]. Similar outcomes might presumably be attributable to other pharmaceuticals as well. Pharmaceutical metabolites and treatment byproducts therefore add to this widely recognized problem.

A potential way to tackle the inconvenience of low concentrations is to process the waters immediately at source points. In practice, this means health-care institutions, with wastewaters containing pharmaceutical contents higher than typical influent at a municipal WWTPs. Treatment before dilution into the public sewage would provide higher concentrations of pharmaceuticals abated in, for example, oxidation reactions, adsorption or reverse osmosis membrane filtration. The last two methods are known, however, together with high operating expenses, for their ability to only redistribute pollutants forming concentrated wastes that require further handling [7].

Various oxidation processes have been widely explored, frequently employing electrochemical methods [8], UV-light in photocatalytic oxidation [9-11], including various reactive oxygen species like ozone (O_3) [12] and hydrogen peroxide (H_2O_2) [13], or shorter living intermediates like hydroxyl (OH) radicals, atomic oxygen $O(^3P)$ and singlet oxygen $O_2(^1\Delta_g)$ [14,15]. The shorter lifetime for the latter group is attributed to their extreme reactivity, which translates as higher oxidation potential. These radical species are desirable in oxidative treatments, collectively known as advanced oxidation processes (AOPs) [16]. Ozonation is one of the most facile and common AOPs; its high price unfortunately restricting its use to rich countries. Ozonation or other AOPs, however, are not commonly assigned for pharmaceuticals destruction at point sources, despite the apparent public awareness of the problem. The natural explanation is of monetary and regulatory disposition; without legislative pressure, the motivation to invest in these solutions remains insufficient.

Many laboratory-scale systems have been developed in efforts to overcome the high cost of ozonation, a variety of non-thermal plasma (NTP) applications among them. Water treatment with NTP can be considered chemically similar to ozonation since these processes include ozone formation from ambient oxygen and OH-radical production from water

molecules, which is also a part of ozone-water reaction kinetics. The most energy-efficient NTP for water treatment has been the gas-phase pulsed corona discharge (PCD), which in the context is usually produced in a wire-plate electrode system in which nano- to microsecond scale high voltage pulses are directed to a metal wire, whose high curvature profile then allows the discharge to initiate and propagate towards the grounded plates [17-20]. The high efficiency of such configuration is based on the non-equilibrium state of ions and free gaseous electrons in the plasma, which means highly energized electrons and excited but low energy molecular or atomic species, resulting in low or negligible heat losses in the overall process. A comprehensive review on pharmaceuticals degradation with NTP applications was reported by Magureanu et al. in [19] and Banaschik et al. in [21], highlighting fast target removal, increased biodegradability and comparable energy costs to other AOPs.

In this study, we examine a pilot-scale PCD unit for reduction of pharmaceuticals content in wastewater before discharge into the public sewage network. The objective is to investigate the feasibility and effectiveness of a PCD water treatment application at point sources with elevated pharmaceutical concentrations. Treatment prior to wastewater discharge to public sewage networks not only holds the potential of higher removal efficiency but also the eventual reduction of sludge contaminants as well, since the overall pharmaceutical content entering the sewage network will be decreased. The PCD is also coupled with ultrafiltration (UF) to investigate whether membrane separation pretreatment would increase PCD efficiency. Earlier, the effectiveness of PCD in oxidation of aqueous carbamazepine in municipal wastewater as well as identified transformation products of the parent compound were shown [22]; this research extends coverage to a wide range of pharmaceuticals in different wastewaters. Wastewaters from two sources in South and South-East Finland were used: raw wastewater from a hospital and effluent from an active sludge wastewater treatment plant of a health institute. Having more extensive pharmaceutical content, the hospital waters receive more detailed discussion, whereas the health institutional wastewater effluent may be considered, for example, as a supporting extension of this investigation.

2. Materials and Methods

2.1 Wastewater Sources

2.1.1 Etelä-Karjala Central Hospital

Etelä-Karjala Central Hospital is a public hospital located in Lappeenranta, Finland, and one of the 16 central hospitals in the country. The hospital works as a comprehensive centralized care unit for South Karelia Social and Health Care District. Annual sewage flow rate data is unfortunately not available. The hospital wastewater samples were pumped from a collective sewer line of the hospital downstream of an oil trap before being discharged into the public sewage network. The piloting was carried out in two sets, for both of which a volume of 1.0 m³ of sewage was separately collected with a tank truck and kept dark and cool through storage. Experiments were conducted and samples delivered for analysis within 48 hours of zero sampling. With the first set (Batch 1), the raw sewage containing suspended solids was allowed to settle in the container for 20 h, after which 350 L was pumped off the top to another container. All the experimental batches were then collected from this volume. From the sewage collected for the second experimental set (Batch 2), a similar initial volume was extracted into a different container through a string wound filter cartridge with a 50 µm filter ratio, after only 3 h settling.

2.1.2 Rinnekoti Foundation

Rinnekoti Foundation in Espoo, Finland, is a center producing healthcare and social inclusion services for people with intellectual or developmental disorders. The institute has its own wastewater treatment plant applying an active sludge process, including denitrification-nitrification steps and chemical phosphorus precipitation. In 2015, the annual treated volume was 114,484 m³ [23]. The plant influent is mainly domestic wastewater collected from the Rinnekoti Foundation facilities, consisting of the daily wastewaters of approximately one thousand people. The wastewater samples from Rinnekoti Foundation were pumped from the effluent stream of the institutional wastewater treatment plant. A total of 1.0 m³ of the treated wastewater was pumped with a submersible pump to a storage container, from which batches of required volume were extracted for the experiments with similar procedures as with the hospital waters. No settling was necessary with the biologically treated wastewaters. Before collecting the zero sample and experimental batches, the water was mixed by circulating the complete volume inside the container for 2 h using the submersible pump. No other pretreatment was applied.

2.2 Analyses

Pharmaceutical concentrations were analyzed by Eurofins Scientific Finland Ltd applying modified EPA methods 1694 and 539 and solid phase extraction. The analysis covered a total of 57 pharmaceutical compounds listed in Table 1. These compounds include clofibric acid, which is more of an active metabolite of etofibrate, etofyllinclofibrate and clofibrate, than a pharmaceutically applied substance [24].

Table 1. The monitored pharmaceuticals and their limit of quantification (LQ). The analytical error at LQ is 30%. ^a = antibiotics, ^b = steroids, ^c = hormones, ^d = NSAID. Analysis was done using ultra-performance liquid chromatograph coupled with tandem mass spectroscopy (UPLC/MS/MS).

Substance	LQ, µg/L	Substance	LQ, µg/L	Substance	LQ, µg/L	Substance	LQ, µg/L
17α-ethinylestradiol ^{bc}	0.001	Enalapril	0.01	Metoprolol	0.02	Progesterone ^{bc}	0.001
17β-estradiol ^{bc}	0.005	Entacapone	0.01	Iopromide	0.01	Propranolol	0.01
Atenolol	0.005	Estriol ^{bc}	0.005	Ketoconazole	0.01	Salbutamol	0.02
Beclometasone	0.005	Estrone ^{bc}	0.005	Ketoprofen	0.005	Simvastatin	0.05
Bezafibrate	0.005	Felodipine	0.05	Methotrexate	0.01	Sotalol	0.01
Bisoprolol	0.01	Fenbendazole	0.005	Methylprednisolone	0.02	Sulfamethoxazole ^a	0.01
Caffeine	0.01	Flubendazole	0.005	Metoprolol	0.005	Terbutaline	0.01
Carbamazepine	0.005	Fluoxetine	0.01	Metronidazole ^a	0.02	Testosterone ^{bc}	0.001
Ciprofloxacin ^a	0.01	Furosemide	0.05	Naproxen	0.01	Tetracycline ^a	0.001
Citalopram	0.01	Gemfibrozil	0.01	Norethindrone ^c	0.02	Trimethoprim ^a	0.01
Clenbuterol	0.005	Hydrochlorothiazide	0.05	Norfloxacin ^a	0.05	Tylosin ^a	0.02
Clofibric acid	0.05	Hydrocortisone ^{bc}	0.01	Ofloxacin ^a	0.05	Warfarin	0.005
Cyclophosphamide	0.005	Ibuprofen ^d	0.05	Oxytetracycline ^a	0.05		
Diclofenac ^d	0.005	Ifosfamide	0.02	Paracetamol	0.05		
Doxycycline ^a	0.02	Iopamidol	0.02	Paroxetine	0.005		

Total organic carbon (TOC) was measured with a Shimadzu TOC L-series analyzer, which applies catalytic combustion at 680 °C. Chemical oxygen demand (COD) was analyzed using potassium dichromate analysis kits and a Hach DR/2000 spectrophotometer. Color and turbidity was measured with a HACH DR/2010- spectrophotometer, at 465 nm and 860 nm, respectively. UV measurements at 254 nm were made using a Jasco V-670 UV-VIS-NIR spectrophotometer. pH was measured with Metrohm 744 pH meter and conductivity with Knick Konduktometer 703.

2.3 Experimental Setup

2.3.1 Plasma Treatment System and Procedure

The PCD system consists of a high voltage pulse generator, a gas-phase corona discharge reactor and a water circulation system. The PCD reactor is of vertical configuration wherein the treated water is allowed a free fall, showering through the NTP. The flow is arranged through a top chamber with a perforated bottom plate with 1-mm orifices. The pulse generator can be adjusted to deliver pulses with a stepwise frequency range from 100 to 840 Hz, which correlates linearly to a nominal power range of 30 to 250 W due to each pulse delivering the energy of 0.3 J. In these experiments, the maximum and the minimum power outputs were used in order to observe the difference between oxidation energy efficiency over maximum available power range. The reactor configuration was coupled with a water circulation system including a tank for 50 L batches. The system is illustrated in Fig. 1. Further details and technical description are presented in our previous publication [25] where the gas-phase ozone concentration in the reactor was also measured, comprising around 5 mg L⁻¹ in air atmosphere, and negligible amounts of oxidants, below 1 mg L⁻¹, were iodometrically measured in the treated water, which was a binary model solution with notably lower amount of oxidant consuming species than in the presently studied sewage.

During experiments, the water was circulated at 15 L min⁻¹ and prior to each sampling the treated volume was allowed to mix by circulating through the system for 5 min with the plasma off. In Batch 1 experiments with hospital wastewater, the treatment at 30 W was applied for 0.1 and 0.5 kWh m⁻³ of pulse energy delivered, and at 250 W for 0.5 and 1.0 kWh m⁻³. For Batch 2, the 30 W treatment was extended to 1.0 kWh m⁻³ following the observed results with Batch 1, to meet better purification results. The energy efficiency of target pollutant oxidation, g kWh⁻¹, was calculated as described elsewhere [18,19] in respect to the removal data.

Figure 1. Experimental PCD configuration for treatment of 50-L batches (not in scale)

2.3.2 Membrane Pretreatment System and Procedures

The membrane filtrations were made using an Alfa Laval DSS LabStak[®] M20-filtration system (Fig. 2), designed for plate-and-frame operations with 0.036 to 0.72 m² membrane areas. Each permeate flow is collected separately from the permeate plate that holds a similar membrane on each side, one plate holding a membrane area 0.036 m². The permeate plates are separated with a plate that distributes the feed flow from the first permeate plate to the next one.

Figure 2. Membrane filtration system (not in scale)

Ultrafiltration of the hospital waters was carried out with UC030 Microdyn-Nadir membranes with an area of 0.144 m^2 at 2.0-3.5 bar. In the experiments with Rinnekoti waters, the same membrane with an area of 0.108 m^2 was used at the pressure of 2.0-2.2 bar. In both cases the cross flow velocity was about 0.7 m s^{-1} .

3. Results and Discussion

3.1 Hospital Wastewaters

Analysis revealed a total of 27 pharmaceuticals in the untreated hospital wastewaters, plus progesterone and methylprednisolone that only occurred in the course of treatment. The two batches of hospital wastewater sported similar pharmaceutical content with minor exceptions: salbutamol ($0.88 \mu\text{g L}^{-1}$), atenol ($2.3 \mu\text{g L}^{-1}$) and warfarin ($0.082 \mu\text{g L}^{-1}$) were only observed in Batch 1 and entacapone ($1.1 \mu\text{g L}^{-1}$) and propranolol ($0.21 \mu\text{g L}^{-1}$) only found in Batch 2. The pharmaceutical content of the wastewater was heavily reduced in PCD treatment, with some deviation in the removal yield as further discussed below. Progesterone, methylprednisolone and ibuprofen exhibited interesting growth in concentration in the course of oxidation, ibuprofen so only momentarily. Tables 2 and 3 present pharmaceuticals removal from hospital waters for Batch 2, which exhibited a tendency for higher initial concentrations of most of the

substances and for which the low power PCD treatment was sustained longer. Results for Batch 1 are included for reference in Supplementary Information Table 1, and the discussion henceforth considers the presented results of Batch 2 unless specifically noted otherwise. Progesterone and methylprednisolone are presented and their occurrence discussed individually in 3.1.2 as they were not present in the untreated water and only occurred as oxidation products. In the following, the results are collectively tabulated and certain peculiarities are separately considered in chapters 3.1.1 to 3.1.3 for deeper scrutinizing; undetected monitored substances are excluded from further presentation.

Table 2. Direct PCD treatment on observed pharmaceutical residues in hospital wastewater Batch 2, complete removal of pollutants (100%) manifests concentrations reduced below LQ

Power Energy, kWh m ⁻³		30 W 0.1		30 W 0.5		30 W 1.0		250 W 0.5		250 W 1.0	
			Removal		Removal		Removal		Removal		Removal
Substance, µg L ⁻¹	Raw	PCD		PCD		PCD		PCD		PCD	
Bisoprolol	0.84	0.6	29%	0.17	80%	<0.10	100%	0.5	40%	0.35	58%
Caffeine	470	450	4%	420	11%	380	19%	480	-2%	480	-2%
Carbamazepine	0.35	0.25	29%	<0.05	100%	<0.05	100%	0.21	40%	0.088	75%
Ciprofloxacin	13	8.6	34%	4.1	68%	0.85	93%	7.2	45%	5.4	58%
Citalopram	0.23	0.17	26%	<0.10	100%	<0.10	100%	0.14	39%	<0.10	100%
Diclofenac	0.6	0.42	30%	<0.05	100%	<0.05	100%	0.26	57%	0.083	86%
Doxycycline	2	1.2	40%	<0.20	100%	<0.20	100%	0.81	60%	0.32	84%
Enalapril	0.31	0.26	16%	0.23	26%	0.19	39%	0.27	13%	0.25	19%
Entacapone	1.1	0.26	76%	<0.10	100%	<0.10	100%	0.18	84%	<0.10	100%
Estriol	0.91	1.1	-21%	<0.05	100%	<0.05	100%	0.49	46%	0.2	78%
Estrone	0.1	0.065	35%	<0.05	100%	<0.05	100%	<0.050	100%	<0.05	100%
Furosemide	11	4.7	57%	<0.50	100%	<0.50	100%	2.6	76%	<0.50	100%
Hydrochlorothiazide	4.2	4.8	-14%	4	5%	2.2	48%	5.4	-29%	4.3	-2%
Hydrocortisone	0.45	0.33	27%	0.43	4%	0.35	22%	0.37	18%	0.37	18%
Ibuprofen	28	34	-21%	24	14%	14	50%	43	-54%	26	7%
Metoprolol	0.37	0.33	11%	0.18	51%	<0.05	100%	0.33	11%	0.26	30%
Metronidazole	8.9	6.6	26%	7.8	12%	7.3	18%	8.1	9%	8.4	6%
Naproxen	1.1	0.78	29%	<0.10	100%	<0.10	100%	0.69	37%	0.5	55%
Ofloxacin	16	11	31%	2.2	86%	<0.50	100%	9.4	41%	5.7	64%
Paracetamol	580	420	28%	70	88%	63	89%	260	55%	130	78%
Propranolol	0.21	0.1	52%	<0.10	100%	<0.10	100%	<0.10	100%	<0.10	100%
Sulfamethoxazole	5.8	2.7	53%	<0.10	100%	<0.10	100%	0.25	96%	<0.10	100%
Tetracycline	1.6	0.83	48%	0.15	91%	0.14	91%	0.59	63%	0.23	86%
Trimethoprim	1.2	0.92	23%	0.061	95%	<0.01	100%	0.73	39%	0.31	74%

Table 3. UF and UF + PCD (30 W) effect on observed pharmaceutical residues in hospital wastewater Batch 2, complete removal of pollutants (100%) manifests concentrations reduced below LQ

Energy, kWh m ⁻³				0.1		0.5		1.0	
Substance, µg L ⁻¹	Raw	UF	Removal	UF+ PCD	Removal	UF+ PCD	Removal	UF+ PCD	Removal
Bisoprolol	0.84	0.74	12%	0.58	31%	<0.10	100%	<0.10	100%
Caffeine	470	440	6%	510	-9%	410	13%	300	36%
Carbamazepine	0.35	0.33	6%	0.28	20%	<0.05	100%	<0.05	100%
Ciprofloxacin	13	8.3	36%	2.6	80%	2	85%	<0.50	100%
Citalopram	0.23	0.18	22%	<0.10	100%	<0.10	100%	<0.10	100%
Diclofenac	0.6	0.68	-13%	0.37	38%	<0.05	100%	<0.05	100%
Doxycycline	2	1.3	35%	<0.20	100%	<0.20	100%	<0.20	100%
Enalapril	0.31	0.21	32%	0.2	35%	0.14	55%	<0.10	100%
Entacapone	1.1	0.67	39%	0.19	83%	<0.10	100%	<0.10	100%
Estriol	0.91	0.65	29%	0.61	33%	<0.05	100%	<0.05	100%
Estrone	0.1	0.076	24%	<0.050	100%	<0.05	100%	<0.05	100%
Furosemide	11	7.3	34%	4.2	62%	<0.50	100%	<0.50	100%
Hydrochlorothiazide	4.2	4.2	0%	3.8	10%	2.2	48%	0.58	86%
Hydrocortisone	0.45	0.42	7%	0.42	7%	0.35	22%	0.26	42%
Ibuprofen	28	27	4%	25	11%	26	7%	16	43%
Metoprolol	0.37	0.37	0%	0.37	0%	0.097	74%	<0.05	100%
Metronidazole	8.9	8.2	8%	8.5	4%	7.3	18%	5.7	36%
Naproxen	1.1	1.2	-9%	0.92	16%	<0.10	100%	<0.10	100%
Ofloxacin	16	12	25%	3.7	77%	<0.50	100%	<0.50	100%
Paracetamol	580	560	3%	400	31%	58	90%	41	93%
Propranolol	0.21	0.16	24%	0.11	48%	<0.10	100%	<0.10	100%
Sulfamethoxazole	5.8	4.8	17%	0.42	93%	<0.10	100%	<0.10	100%
Tetracycline	1.6	1.5	6%	0.14	91%	<0.10	100%	<0.10	100%
Trimethoprim	1.2	1.2	0%	0.95	21%	0.01	99%	<0.01	100%

Tables 2 and 3 show that ibuprofen, a common pain killer and NSAID, increases momentarily in concentration in certain PCD experiments (similar observations in Batch 1). Fast oxidation of the substance in the same process at higher concentrations in model solutions was reported earlier [18], suggesting that the slow reduction of ibuprofen in the present case probably overlapped with reformation from oxidation of metabolites. This would suggest that the actual removal rates cannot be accurately estimated in the context of real wastewaters without negative bias from simultaneous reformation. The suggestion that ibuprofen indeed is reforming from transformation products is supported by Ferrando-Climet et al. [26], where a number of ibuprofen metabolites were identified in WWTP influent totaling substantially more abundant than the parent substance.

3.1.1 Paracetamol and Caffeine

Paracetamol and caffeine were distinguished with two to three orders of magnitude higher concentrations than the other monitored substances. Paracetamol, abundant as common painkiller, was reduced by 93% with UF + PCD at 30. Direct PCD treatment achieved 89-% reduction at best, corresponding to a yield of 517 mg kWh⁻¹. For reference, Panorel et al. reported 40 times higher yield of 20 g kWh⁻¹ for paracetamol, with the same process in a binary model solution at two orders of magnitude higher initial concentration [18]. Although vaguely comparable in light of the experimental concentration difference, the similar response emphasizes the non-selective character of PCD treatment in successful operation with clean water solutions and wastewater. The results support previous findings on PCD treatment of municipal wastewater effluent [22].

Caffeine, a nervous stimulant [27], is a ubiquitous ingredient in common refreshments and naturally present in over 60 plants [28]. Caffeine proved more resilient to oxidation than paracetamol which could be anticipated due to the strong molecular structure with concise nitrogen bonding and ketone groups: the vacancy available for the OH-radical or ozone attack, the C=N bond, is characterized by relatively high energy of 615 kJ mol⁻¹. Beltrán et al. [29] stated that caffeine is oxidized predominantly with OH-radicals and refractory to oxidation with molecular ozone. Siqueira Souza and Amaral Férís [30], Broséus et al. [31] and Ganzenko et al. [32] confirmed these observations in various AOPs with hard mineralization. A series of publications reported caffeine being oxidized more effectively in combination of ozone with catalysts and photocatalytic oxidation [33-36]. Analogously, dielectric barrier discharge (DBD) exhibited efficiency improved by a goethite catalyst [37]. Rosal et al. [38] disclosed a mechanism of caffeine ozonation with both ozone and OH-radicals indicating rather low second-order reaction rate constant ranging from 0.25 to 1.05 M⁻¹ s⁻¹ and increasing with pH from 3 to 10, i.e. at improving OH-radical contribution in oxidation; the reaction rate constant for OH-radical formation in the reaction of ozone with OH-ion is 70 M⁻¹ s⁻¹ [39]. In comparison, the phenyl moiety in paracetamol (Scheme 1) assumes facile oxidation [40]. The poor removal efficiency of caffeine, however, conveniently proposes little disappointment due to its biodegradability: it is reported to degrade at 94% average efficiency in conventional WWTPs [41], ranging even above 99% [42].

Scheme 1. Molecular structures of caffeine (left) and paracetamol (right). The refractory nature of caffeine is obvious from the strong N- and O-bonding

3.1.2 Antibiotics

Antibiotics can be largely unaffected in conventional WWTPs [43] and pose a special and generally recognized problem for potent development of bacterial resistance [44,45]. Removal in active sludge processes may be largely attributed to sorption in the sludge [46], which does not remove the problem. Concise and multi-reference description of accumulated antibiotics in the environment is given in [47]. In this study, doxycycline, metronidazole, ofloxacin, ciprofloxacin, sulfamethoxazole, tetracycline and trimethoprim were found in the hospital wastewaters at concentrations ranging from 1.2 to 13 $\mu\text{g L}^{-1}$. The best result was achieved with the UF + PCD (30 W) process at 1.0 kWh m^{-3} where all the antibiotics were completely oxidized, except metronidazole (36-% reduction), which proved highly resilient to oxidation. The refractory nature of metronidazole is a characteristic of the concise molecular construction with two amines in the cycle and a nitro group (Scheme 2). Mota et al. [48] described oxidation of metronidazole with ozone starting from the high-energy C=N bond adjacent to the nitro-group analogously to the caffeine primary oxidation act. Previous studies showed refractory character of metronidazole towards oxidation with ozone, being improved with catalytic aid of activated carbons [49] and in combination with photocatalysis [50]. Considering the overall antibiotics oxidation result, improvement from ultrafiltration pretreatment was pronounced at lower energy doses: by 32, 11 and 5% higher total antibiotics removal at 0.1, 0.5 and 1.0 kWh m^{-3} , respectively.

Scheme 2. Molecular structure of metronidazole

3.1.3 Pharmaceuticals Appearing during PCD Oxidation

Progesterone and methylprednisolone, both steroidal hormones sharing structural similarity, appeared only during PCD oxidation of the hospital wastewaters and consistently increased in concentration throughout the pulsed energy delivery. The observed increase is an apparent recurrence: the result of oxidation of metabolites, e.g. cysteine conjugates [51], transforming back to the parent compound. Neither of the substances were observed in samples prior to treatment. The recurrence phenomenon resembles biological oxidation of carbamazepine metabolites in wastewater treatment transforming back into carbamazepine [4], although be it noted that carbamazepine concentrations only decreased in PCD-oxidation both in the present study and in [22]. A decreasing concentration was not observed for either substance within the extent of the experiments, suggesting the concentrations of the precursors exceed that of the observed parent compound maxima. Since degradation of organic compounds is generally an oxidation process, the observed formation of progesterone and methylprednisolone during PCD treatment proposes a possibility of these reactions taking place in common WWTPs as well, similarly as reported for carbamazepine. Besides, even though progesterone and methylprednisolone were observed to actually increase in the process, it should be noted that these are oxidation products and therefore assumable intermediate products in naturally occurring degradation pathways as well.

Progesterone, initially below the level of detection, was also not observed at the lowest energy dose of 0.1 kWh m^{-3} , which, as noted above, was well sufficient for effective reduction of many of the monitored substances. At low treatment power, the first occurrence was at 0.5 kWh m^{-3} and at full power the concentration was measurable only at the end at 1 kWh m^{-3} . Here, a maximum progesterone concentration after PCD treatment was measured as $0.072 \text{ } \mu\text{g L}^{-1}$ at 30 W pulse power, while at 250 W the amounts remained at $0.017\text{-}0.021 \text{ } \mu\text{g L}^{-1}$, approximately four times lower at eight

times higher pulse power. The disproportion between the rates and applied powers would suggest ozone has a notable role in the reactions [25]. The maximum value corresponds to a progesterone yield of $72 \mu\text{g kWh}^{-1}$. The well-known metabolite, allopregnanolone, is suggested as a probable candidate for the main progesterone precursor in the oxidative conditions, having a hydroxyl group prone for oxidation by the abundant hydroxyl radicals. A comprehensive list of identified and theoretical metabolites of progesterone can be found in the article by Stanczyk [52]. Similar to testosterone, Fabre et al. [51] reported cysteine conjugates as progesterone metabolites. Since progesterone was not found from the first treated samples, regardless of plasma power, it is suggested that there may be multiple reaction steps until the parent compound is reformed, which could infer that the presence of metabolites changed beyond allopregnanolone that is still relatively similar with the parent compound. The development of progesterone concentrations in direct PCD treatment of the hospital waters is presented in Fig. 3. Peculiarly, no progesterone was observed in ultrafiltered and subsequent PCD samples, which may indicate adsorption properties in sedimentary material; indeed, Sangster et al. [53] described different progesterone spiked sediment materials resulting in essentially varied effects upon fish population in the given environment. The destruction of pharmaceutical metabolites is of equal importance with the destruction of the parent compounds, as, for example, the suggested precursor allopregnanolone is also highly bioactive [54].

Figure 3. Evolution of progesterone in direct PCD treatment of the hospital wastewater Batches 1 and 2: ■ = Batch 1; ▲ = Batch 2; solid line = 250 W PCD; dashed line = 30 W PCD

Methylprednisolone concentration increased in both ultrafiltered and unfiltered hospital waters subjected to oxidation. A peak concentration of $1.4 \mu\text{g L}^{-1}$ was recorded for methylprednisolone with the maximum energy dose at 30 W pulse power, which corresponds to a yield of $1400 \mu\text{g kWh}^{-1}$. A comprehensive collection of 15 methylprednisolone metabolites was reported by Pozo et al. [55], proposing a list of precursor candidates whose oxidation would result in reformation of the parent compound. The most probable of these candidates would be the products of one-step reduction, which was suggested to occur at the keto moiety of the aliphatic carbon chain of the molecule.

Methylprednisolone concentrations in PCD treated hospital waters are presented in Fig. 4.

Figure 4. Evolution of methylprednisolone in PCD treatment of hospital wastewater batches 1 and 2 with and without ultrafiltration: ■ = Batch 1; ▲ = Batch 2; solid line = 250 W PCD; dashed line = 30 W PCD; frequently dashed line = ultrafiltration and 30 W PCD

3.1.4 Total Pharmaceutical Compound Removal

The mass-based occurrence of total detected pharmaceuticals amounted to $1,148 \mu\text{g L}^{-1}$, $678 \mu\text{g L}^{-1}$ without caffeine and $98 \mu\text{g L}^{-1}$ without caffeine and paracetamol, the two individual substances thus constituting a substantial 91% of the total pharmaceutical mass. Calculations for maximum reduction achieved from these values with UF, PCD and their combination are presented in Table 4.

Table 4. Total pharmaceutical occurrence and maximum removal rate at PCD energy 1.0 kWh m^{-3}

	Content, $\mu\text{g L}^{-1}$	Removal (%)			
		UF	UF + PCD 30 W	PCD 30 W	PCD 250 W
Total	1148.27	6	68	59	42
w/o caffeine	678.27	5	91	87	73
w/o caffeine and paracetamol	98.27	17	77	75	46

Regardless of the noticeable removal of pharmaceuticals with UF, up to 17% if the reduction of other than caffeine and paracetamol is considered, contribution of preliminary UF to the sum effect with PCD was modest. The results propose the overall pharmaceuticals removal fitting to 9% difference whether UF is used as pretreatment before PCD or not - 68% and 59% of total pharmaceuticals removed at 30 W applied power at PCD energy input of 1.0 kWh m^{-3} with and without preliminary UF, respectively. The effect of preliminary UF was even smaller for pharmaceuticals considered with caffeine and caffeine together with paracetamol subtracted, 4% and 2%, respectively. This implies that as a combined unit process, UF pretreatment had very modest effect on the overall efficiency of PCD oxidation. Comparing a noticeable difference of the UF effect observed for antibiotics (see 3.1.2), an attractive solution for cutting the environmental load by pharmaceuticals with antibiotics deserves special emphasis in further research in PCD combination with UF.

The rate of PCD energy delivery expectedly makes a difference showing substantially positive effect at low pulse repetition frequency, i.e. smaller applied power explained by the contribution of ozone to the oxidation effect at longer treatment times (Table 4). The trade-off, however, involves longer time required at more energy-effective low-power treatment.

3.1.5 Wastewater Characterization

The effect of membrane processes was expectedly more pronounced on other characteristics of the wastewater, TOC (30%), COD (37%), UV-absorption (20%) and color. Ultrafiltration alone resulted in 69-% reduction in turbidity and 63-% reduction in color; combined with PCD oxidation these results were 87% for both parameters. For comparison, PCD alone reduced turbidity by 47% and color by 58% via oxidative bleaching. A mild increase in conductivity can be observed during PCD treatment, which is likely a result of nitrate formation during the process from ambient nitrogen [56]. These results are presented in Supplementary Information Table 2 with other characteristic parameters.

3.1.6 Maintenance

Clogging of the perforation through which the water is introduced into the plasma reactor might be the most potential problem, and be it noted that in this work, settling (and string filtration for Batch 2) of the raw hospital sewage likely aided this cause. Yet, no maintenance requirements have been recognized by the authors, considering the reactor configuration designed for water treatment, or the pulse generator supplying the high voltage power. Membrane fouling, however, is a well-recognized characteristic. Here, in any membrane separation process the permeate flow immediately decreased from initial condition. Nonetheless, in each case permeability settled to a certain level during filtration and the membranes were restored to original permeability with post-process washing using commercial P3-Ultrasil 110 detergent by Ecolab. Membrane performance data is presented in more detail in Supplementary Information Fig. 1.

3.2 Health Institutional Wastewaters

A total of 17 of the monitored pharmaceutical substances were found in the biologically treated wastewater effluent of Rinnekoti Foundation. Of these, carbamazepine, a widely used antiepileptic substance, occurred at a concentration an order of magnitude higher than any other observed substance, which may be explained by the institutional provision of services for the inhabitants with physical disorders. Additionally, ibuprofen was observed only at $0.082 \mu\text{g L}^{-1}$ in the first treated sample of the 250 W direct PCD experiment, at 0.5 kWh m^{-3} energy delivered. This momentary appearance aligns similarly with the hospital waters, the briefly occurring low concentration disappearing along further treatment (introduced here, ibuprofen is omitted from the following tables for conciseness). Direct PCD and combined UF + PCD results in pharmaceuticals removal are presented in Tables 5 and 6, respectively.

Table 5. Direct PCD treatment on observed pharmaceutical residues in biologically treated health institutional wastewater effluent, complete removal of pollutants (100%) manifests concentrations reduced below LQ

Power Energy, kWh m^{-3}		30 W 0.1		30 W 0.5		250 W 0.5		250 W 1.0	
			Removal		Removal		Removal		Removal
Substance, $\mu\text{g L}^{-1}$	Raw	PCD		PCD		PCD		PCD	

Bisoprolol	0.18	0.038	79%	<0.010	100%	0.022	88%	<0.010	100%
Caffeine	0.012	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Carbamazepine	3.1	0.013	100%	<0.005	100%	0.011	100%	<0.005	100%
Citalopram	0.26	0.048	82%	<0.010	100%	0.028	89%	<0.010	100%
Diclofenac	0.33	<0.005	100%	<0.005	100%	<0.005	100%	<0.005	100%
Fluoxetine	0.068	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Furosemide	0.29	<0.050	100%	<0.050	100%	<0.050	100%	<0.050	100%
Hydrochlorothiazide	0.83	0.32	61%	<0.050	100%	0.14	83%	<0.050	100%
Ketoprofen	0.022	0.009	59%	<0.005	100%	<0.005	100%	<0.005	100%
Metoprolol	0.44	0.13	70%	<0.005	100%	0.066	85%	<0.005	100%
Metronidazole	0.059	0.034	42%	<0.020	100%	<0.020	100%	<0.020	100%
Naproxen	0.082	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Propranolol	0.23	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Salbutamol	0.2	<0.020	100%	<0.020	100%	<0.020	100%	<0.020	100%
Sotalol	0.14	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Trimethoprim	0.036	<0.001	100%	<0.001	100%	<0.001	100%	<0.001	100%
Warfarin	0.007	<0.005	100%	<0.005	100%	<0.005	100%	<0.005	100%

Table 6. UF and UF + PCD effect on observed pharmaceutical residues in biologically treated health institutional wastewater effluent, complete removal of pollutants (100%) manifests concentrations reduced below LQ

Power Energy, kWh m ⁻³				30 W 0.1		30 W 0.5		250 W 0.5		250 W 1.0	
Substance, µg L ⁻¹	Raw	UF	Removal	UF+PCD	Removal	UF+PCD	Removal	UF+PCD	Removal	UF+PCD	Removal
Bisoprolol	0.18	0.17	6%	0.021	88%	<0.010	100%	0.017	91%	<0.010	100%
Caffeine	0.012	0.013	-8%	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Carbamazepine	3.1	2.9	6%	<0.005	100%	<0.005	100%	<0.005	100%	<0.005	100%
Citalopram	0.26	0.22	15%	<0.010	100%	<0.010	100%	0.011	96%	<0.010	100%
Diclofenac	0.33	0.32	3%	0.012	96%	<0.005	100%	<0.005	100%	<0.005	100%
Fluoxetine	0.068	0.023	66%	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Furosemide	0.29	0.3	-3%	<0.050	100%	<0.050	100%	<0.050	100%	<0.050	100%
Hydrochlorothiazide	0.83	0.58	30%	0.07	92%	<0.050	100%	0.065	92%	<0.050	100%
Ketoprofen	0.022	0.016	27%	0.006	73%	<0.005	100%	<0.005	100%	<0.005	100%
Metoprolol	0.44	0.43	2%	0.076	83%	<0.005	100%	0.052	88%	<0.005	100%
Metronidazole	0.059	0.064	-8%	0.028	53%	<0.020	100%	<0.020	100%	<0.020	100%
Naproxen	0.082	0.12	-46%	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Propranolol	0.23	0.19	17%	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Salbutamol	0.2	0.18	10%	<0.020	100%	<0.020	100%	<0.020	100%	<0.020	100%
Sotalol	0.14	0.16	-14%	<0.010	100%	<0.010	100%	<0.010	100%	<0.010	100%
Trimethoprim	0.036	0.033	8%	<0.001	100%	<0.001	100%	<0.001	100%	<0.001	100%
Warfarin	0.007	0.008	-14%	<0.001	100%	<0.005	100%	<0.005	100%	<0.005	100%

All the studied pharmaceuticals, including hydrochlorothiazide and metronidazole (initial concentrations close to LQ), were substantially reduced with PCD at the minimum energy dose ($250\text{ W} - 0.5\text{ kWh m}^{-3}$; $30\text{ W} - 0.1\text{ kWh m}^{-3}$) and completely disappeared at maximum ($250\text{ W} - 1\text{ kWh m}^{-3}$; $30\text{ W} - 0.5\text{ kWh m}^{-3}$). This would suggest that biologically treated wastewater enables a more targeted oxidation process, i.e. less oxidants consumed in unwanted reactions than in the complex matrix of untreated sewage. The total pharmaceutical content is also lower in the biologically treated wastewater than in the untreated hospital sewage. In addition, albeit from different sources, the biodegradability of caffeine was apparent from the concentrations of the untreated hospital sewage and the biologically treated Rinnekoti effluent, demonstrating four orders of magnitude difference.

The results with Rinnekoti waters clearly show that the present PCD configuration can, in a realistic case, be effective as a tertiary treatment process for polishing wastewaters from medicinal pollutants before discharge into the environment. The total mass concentration of the detected pharmaceuticals in the effluent amounted to $6.286\text{ }\mu\text{g L}^{-1}$, which was practically completely removed with direct PCD treatment at 0.5 kWh m^{-3} , yielding 12.6 mg kWh^{-1} total drug removal. For perspective, for the annual reported flow through the plant this would correspond to an annual energy consumption of $57\,242\text{ kWh}$, which at a rounded estimate of electricity price of 0.1 € kWh^{-1} and pulse generator efficiency of 67% [18] would result in a cost of $\text{€}8,543$. Specific energy dose of 0.1 kWh m^{-3} , at which 91-% reduction of total pharmaceuticals was achieved (97% w/ UF + PCD), gives an annual cost of $\text{€}1,709$. The annual volume discharge with the observed concentrations would give a total of 720 g pharmaceuticals discharged to the aquatic environment, which gives an impression of relatively high cost versus absolute pharmaceuticals reduction. It should be stressed, however, that the estimated yields only consider the monitored substances, and do not include the non-selectively affected compounds of medicinal or any other origin, including the pharmaceuticals transformed beyond detection while retaining biological activity. This demonstration well describes the challenges intrinsic in chemical micropollutant abatement, the cost profile exponentially increasing with removal of decreasing concentrations. As presented, however, notable results are feasible at acceptable cost range.

4. Conclusions

A pilot-scale pulsed corona discharge (PCD) plasma was applied to oxidize micro-concentrations of pharmaceuticals in wastewaters collected at point sources. The PCD process was tested for both untreated sewage of a public hospital and for biologically treated wastewater effluent of a healthcare institute. In the hospital wastewaters, almost all of twenty-nine detected pharmaceuticals were readily oxidized: caffeine, hydrochlorothiazide and metronidazole exhibited strong resilience. Caffeine and paracetamol occurred in two to three orders of magnitude higher concentration than other pharmaceuticals. Of these, caffeine is readily biodegradable, which was emphasized by four orders of magnitude lower initial concentration in the biologically treated effluent.

The oxidation process was coupled with 30 kDa ultrafiltration pretreatment to investigate the effect of the separation process on oxidation energy efficiency of the PCD: UF had little effect on total pharmaceuticals content, excluding caffeine, in hospital waters (5-% reduction), improving the total result of UF + PCD by 4% when compared to sole PCD at 1 kWh m⁻³ energy consumption. The oxidation resulted in 90-% reduction from the UF permeate concentration, which is only a 3-% improvement compared to oxidation of the raw sewage.

Reformation of progesterone and methylprednisolone was observed during the oxidation process; a phenomenon that has been observed for a few other pharmaceuticals earlier, where metabolites oxidize back to the parent compound. Similar behavior was observed for ibuprofen.

With the biologically treated wastewater effluent, a substantial effect in micropollutant removal was seen already at 0.1 kWh m⁻³, and at 0.5 kWh m⁻³ all the seventeen observed pharmaceuticals were oxidized below the limit of quantification. The result was more polished than as with the raw hospital wastewater sewage, due to the essentially lower concentrations of competing non-medical pollutants. The PCD efficiency in the raw sewage, however, is of emphasized importance as the volumes requiring treatment at such point source will obviously remain smaller and concentrations higher than those compiled at the influent of wastewater treatment sites. The non-selective pharmaceuticals reduction process will be inherently more efficient at locations of higher concentrations, leading to substantially reduced pharmaceutical load to the environment at the end of the pipe.

The capital cost assessment for the PCD treatment is unavailable currently for the absence of this technology at the market so far, the technology is developing at its piloting stage. Oxidative treatment, however, is a more final solution for micropollutants than e.g. adsorption redistributing the pollution for further handling of hazardous solid wastes.

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