OXIDATION OF AQUEOUS PHARMACEUTICALS WITH PERSULFATE ACTIVATED BY NON-THERMAL PLASMA

Dmitri Nikitin, Eneliis Kattel-Salusoo, Sergei Preis, Niina Dulova*

Tallinn University of Technology, Department of Materials and Environmental Technology, Ehitajate tee 5, 19086 Tallinn, Estonia

Abstract

The oxidation of antibiotic vancomycin (VAN), antidiabetic metformin (MET), and anti-inflammatory dexamethasone (DEX) was studied using a combined pulsed corona discharge (PCD) and persulfate (PS) system. The effect of the dose of persulfate on the degradation rate, the degree of mineralization, and the energy efficiency of the target pharmaceuticals oxidation was evaluated. Irrespective of the target compound studied, the addition of moderate persulfate doses resulted in a noticeable improvement in oxidation efficiency compared to non-assisted PCD process. For all pharmaceuticals examined, with minor exception for DEX showing negligible improvement, an increase of the dose of persulfate in the PCD/PS combination resulted in a substantial increase in the observed degradation rate. The findings of this study strongly suggest that the combined PCD/PS oxidation is a promising treatment technology for water purification from aqueous pharmaceutical contamination.

Keywords: *advanced oxidation process; peroxydisulfate; pulsed corona discharge, water treatment*

1. INTRODUCTION

An increase in the production and consumption of pharmaceuticals inevitably leads to their accumulation in surface and groundwater [1]. Such a widespread contamination of aquatic environments with pharmaceutical residues primarily indicates their incomplete removal from wastewater at wastewater treatment plants (WWTPs). As a result, alternative or additional treatment methods are needed to improve the quality of WWTPs effluents discharged into the environment. A promising solution to this problem is the use of advanced oxidation processes (AOPs) based on hydroxyl ($HO^{\bullet}$) and/or sulfate ($SO_4^{\bullet-}$) radicals, which have proven effective in removing various contaminants of emerging concern that occur in water [2,3].

Non-thermal gas-phase pulsed corona discharge (PCD) is one of the hydroxyl radicals-based AOPs. This discharge surpasses other plasma types in energy efficiency due to the formation of hydroxyl radicals (E^0=2.8 V) [2] at the surface of treated aqueous solution, i.e., in close vicinity of the target pollutants experiencing negligible resistance in diffusion into the aqueous phase [4]. Except for hydroxyl radicals, atomic oxygen, ozone, hydrogen peroxide and other reactive species participate in PCD oxidation (Eqs. (1)-(4)) [5,6].

$$O_2 + e^- \rightarrow 2O^{\bullet} + e^- \quad (1)$$

$$O^{\bullet} + O_2 + O_2 \text{ (or } N_2) \rightarrow O_3 + O_2 \text{ (or } N_2) \quad (2)$$

$$H_2O + e^- \rightarrow HO^{\bullet} + H^{\bullet} + e^- \quad (3)$$

$$HO^{\bullet} + HO^{\bullet} \rightarrow H_2O_2 \quad (4)$$

The addition of persulfate (PS, peroxydisulfate, $S_2O_8^{2-}$) has been actively studied for other types of plasma, such as double barrier discharge, which has made it possible to achieve increased degradation rates for various organic pollutants [7,8]. The main advantages of sulfate radicals over hydroxyl ones include a higher redox potential (E^0=2.6-3.1 V) [9], a wider operating pH range, selectivity of reactions with target pollutants, and increased oxidative capacity in phosphate and carbonate buffer solutions [10].

In this study, vancomycin (VAN), metformin (MET), and dexamethasone (DEX) were selected as representatives of different drug classes to evaluate the effectiveness of the PCD-activated PS system for aqueous pharmaceuticals oxidation. VAN is an amphoteric glycopeptide antibiotic used to treat

infections caused by Gram-positive organisms [11]. Vancomycin and its modifications are considered drugs of last resort, that is, the last line of defense against resistant pathogens [12]. MET is a common drug used in the treatment of type 2 diabetes, which is frequently detected in the aquatic environment [13]. Despite the low acute toxicity of MET, it acts as an endocrine disruptor to non-target organisms at environmentally relevant concentrations [14]. DEX is one of the most prescribed synthetic glucocorticoids [15]. DEX is also an endocrine disruptor, has a fluorine atom in its molecular structure, making it environmentally hazardous and virtually non-biodegradable [16].

Therefore, the aim of the current study was to evaluate and compare the effect of persulfate and its concentration on the overall treatment efficacy and the energy efficiency of the oxidation of selected pharmaceuticals in combination with gas-phase pulsed corona discharge.

2. MATERIALS AND METHODS

2.1. Materials

Dexamethasone ($C_{22}H_{29}FO_5$, 98%) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$, >97%) were purchased from Alfa Aesar. Vancomycin hydrochloride ($C_{66}H_{75}Cl_2N_9O_{24} \cdot xHCl$, ≥99%), ethanol ($C_2H_6O$, 99%), methanol ($CH_3OH$, ≥99%), acetonitrile ($CH_3CN$, LiChrosolv®, ≥99.9%), and formic acid (CH_2O_2, 99%) were obtained from Merck KGaA. Sodium persulfate ($Na_2S_2O_8$, ≥99%) and sodium sulfite (Na_2SO_3, 99%) were supplied from Sigma-Aldrich.

2.2. Experimental procedure

The PCD and PCD/PS experiments were conducted in a device shown in Fig. 1, with detailed characteristics given in Table 1 (Reactor I for DEX and MET trials, Reactor II for VAN trials). Briefly, the plasma reactor comprises an electrode system consisting of high voltage wire electrodes placed horizontally between two grounded vertical parallel plates. The pulse generator delivers high voltage pulses to the electrode system. The output-input ratio of the pulse generator comprises 65%. The treated solution is distributed through a perforated plate positioned above the wire electrodes. After passing the plasma zone, the treated solution falls to a storage tank, from where it circulates back to the top of the reactor.

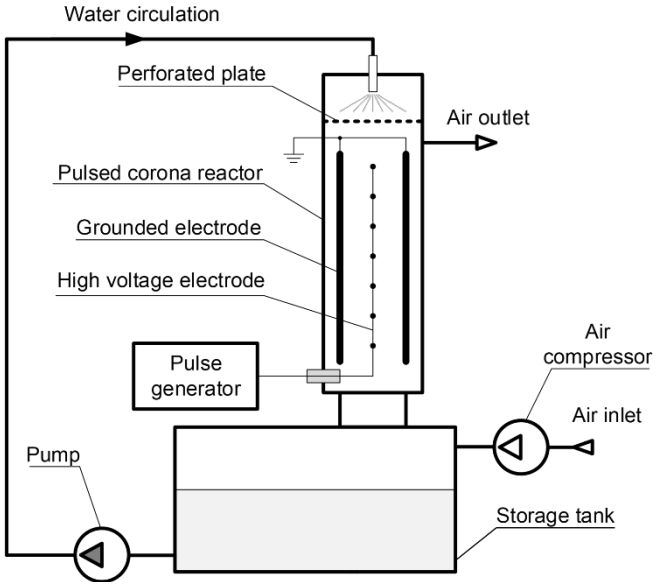

Fig. 1. Scheme of PCD reactor

The experiments were carried out at ambient room temperature of 22 ± 2°C, at the initial concentration of VAN, MET, and DEX of 13.5, 60.4, and 25.5 μM, respectively. Stock solutions were prepared in a 1-L volumetric flask using bi-distilled water, followed by dilution to a total working solution volume of 5 L (for DEX and VAN) or 10 L (for MET) by distilled water in the reactor tank. The unadjusted pH value of the prepared working solutions was 6.8 ± 0.2, 6.5 ± 0.2, and 6.6 ± 0.2 for VAN, MET, and DEX, respectively. Pre-selected amounts of persulfate were dissolved in a 100-mL volumetric flask and mixed to the working solution in the tank before the start of treatment.

The PCD and PCD/PS experiments for VAN, MET, and DEX oxidation were performed at a circulated water flow rate of 1 m^3/h and the pulse repetition frequency of 50, 50 and 200 pulses per second with the power input of 8, 9, and 32 W, respectively. Plasma treatment time comprised 1 h (for DEX) and 2 h (for MET and VAN) with total energy dose of 6.4 kWh/m^3, 1.8 kWh/m^3 and 3.2 kWh/m^3 delivered to the treated sample, respectively. For proper sampling, the treated solutions were circulated in the reactor for four minutes after the pulse generator was turned off to equalize the concentrations in the reactor's volume.

Table 1. Technical parameters of PCD reactors

Parameter	Reactor I	Reactor II
Reactor parameters		
Reactor full volume, L	110	80
Perforated plate size, mm × mm	500 × 30	565 × 97
Number of perforations	51	24
Diameter of perforations, mm	1	3
Water flow rate, L/min	2-28.5	2-18
Spray density, m/s	0.002-0.0243	0.002-0.0177
Plasma zone volume, m^3	0.013	0.011
Contact surface area at flow rate of 1 m^3/h, 1/m	91.9	130
Electrode configuration		
High voltage wire length, m	20	12
Wire diameter, mm	0.55	0.6
Distance between electrodes and grounded plate, mm	18	17
Distance between high-voltage electrodes, mm	30	30
Generator characteristics		
Pulse repetition frequency, pps	50-880	25-800
Output power, W	9-123.2	8-112
Peak voltage, kV	18	22
Peak current, A	380	290
Current pulse duration, ns	100	70
Pulse energy, J	0.14-0.18	0.14-0.16

The oxidation reaction in PCD/PS combinations was quenched with ethanol or methanol added at the alcohol/sample volume ratio of 1/10, or Na_2SO_3 at a persulfate/sulfite molar ratio of 1/10 for HPLC and TOC analyses, respectively.

2.3 Analytical methods

The concentration of DEX and VAN was quantified using HPLC combined with diode array detector (HPLC-PDA, Shimadzu SPD-M20A) equipped with equipped with a Phenomenex Gemini (150 × 2.0 mm, 1.7 mm) NX-C18 (110 Å, 5 µm) column. The analysis was performed using an isocratic method with a mobile phase mixture of 40% acetonitrile containing 0.3% of formic acid and 60% of 0.3% formic acid aqueous solution for DEX and of 9% acetonitrile containing 0.3% of formic acid and 60% of 0.3% formic acid aqueous solution for VAN. Samples (75 µL) were analyzed at the flow rate of 200 µL/min and 250 µL/min for DEX and VAN, respectively.

MET concentration was quantified using HPLC with the same chromatographic column combined with mass spectrometer (HPLC-MS, Shimadzu LC-MS, 2020). The isocratic eluent mixture was composed of 10% acetonitrile containing 0.3% of formic acid and 90% of 0.3% formic acid aqueous solution. The flow rate was kept at 200 µL/min. Mass spectra were acquired in full-scan (50–500 m/z) and SIM (130 m/z) modes. The instrument was operated in positive ESI mode, and the results obtained with MS detector were handled using Shimadzu Lab Solutions software.

Total carbon (TC) and total inorganic carbon (TIC) were measured using a TOC analyzer multi N/C® 3100 (Analytik Jena, Germany) in 20-mL samples with an injection volume of 500 µL for each replicate. Total organic carbon (TOC) was calculated as the difference between TC and TIC. Solution pH was measured using a digital pH/Ion meter (Mettler Toledo S220).

3. RESULTS AND DISCUSSION

To evaluate the effect of persulfate addition on the target pharmaceuticals degradation efficiency, an observed pseudo-first-order reaction rate constant k_{obs} was calculated (Eq. (5)) using slopes of the straight lines by plotting ln (C_t/C_0) as a function of delivered energy dose D (Eq. (6)) through linear regression:

$$d[C]/dD = -k_{obs} \cdot [C] \quad (5)$$

$$D = P \cdot t/V \quad (6)$$

where k_{obs} – the observed pseudo-first order reaction rate constant, m^3/kWh; C – concentration of target compound; D – delivered energy dose, kWh/m^3, P – power delivered in PCD treatment, kW; V – volume of treated solution, m^3.

The results of blank persulfate oxidation experiments at unadjusted pH without applying PCD indicated no significant changes (≤ 5%) in VAN, MET, and DEX concentrations. In turn, the application of non-assisted PCD treatment resulted in k_{obs} values of 30.3, 2.3 and 3.3 m^3/kWh, respectively (Figs. 2-4).

The effect of pH on VAN oxidation within acidic to circumneutral, i.e., unadjusted conditions interval was negligible for the non-assisted PCD. On the other hand, for MET and DEX the observed degradation rate was higher at pH 3 with k_{obs} values of 3.3 and 7 m^3/kWh, respectively. It is noteworthy that in the acidic media, the pH remained almost constant during the treatment, while in the circumneutral media it decreased to < 4 after 1 h of treatment. The observed decrease in the pH value during PCD experiments is mainly associated with the formation of nitric acid [13] and acidic by-products of target pharmaceuticals oxidation [18]. Due to the inevitable decrease in circumneutral pH during PCD treatment, PCD/PS combinations were studied without pH adjustment. The results of VAN, MET, and DEX oxidation in combined PCD/PS systems are shown in Figs. 2-4.

In the PCD/PS combination, persulfate can be activated by a pulsed electric field, ultraviolet radiation, and reactive species formed in the plasma, such as e_{aq}^-, $HO^\bullet$, $H^\bullet$, $HO_2^\bullet$, and $O_2^{\bullet-}$ (Eqs. (7)-(12)) [7,19].

$$e_{aq}^- + S_2O_8^{2-} \rightarrow SO_4^{\bullet-} + SO_4^{2-} \quad (7)$$

$HO^{\bullet} + S_2O_8^{2-} \rightarrow SO_4^{\bullet-} + HSO_4^{-} + 0.5O_2$ (8)

$HO_2^{\bullet} + S_2O_8^{2-} \rightarrow SO_4^{\bullet-} + SO_4^{2-} + O_2 + H^+$ (9)

$O_2^{\bullet-} + S_2O_8^{2-} \rightarrow SO_4^{\bullet-} + SO_4^{2-} + O_2$ (10)

$S_2O_8^{2-} + hv \rightarrow 2SO_4^{\bullet-}$ (11)

$H_2O_2 + S_2O_8^{2-} \rightarrow 2SO_4^{\bullet-}$ (12)

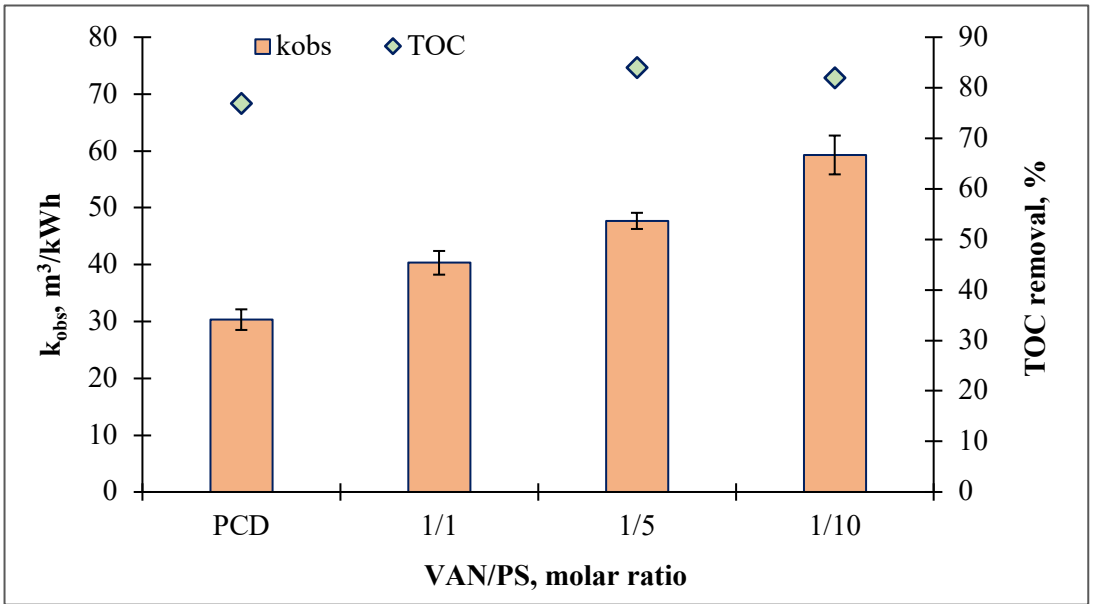

Fig. 2. Effect of VAN/PS molar ratio on the k_{obs} and TOC removal in VAN oxidation by PCD and PCD/PS combination ($[VAN]_0$ = 13.5 μM, PCD output power 8 W, t_{TOC} = 2 h)

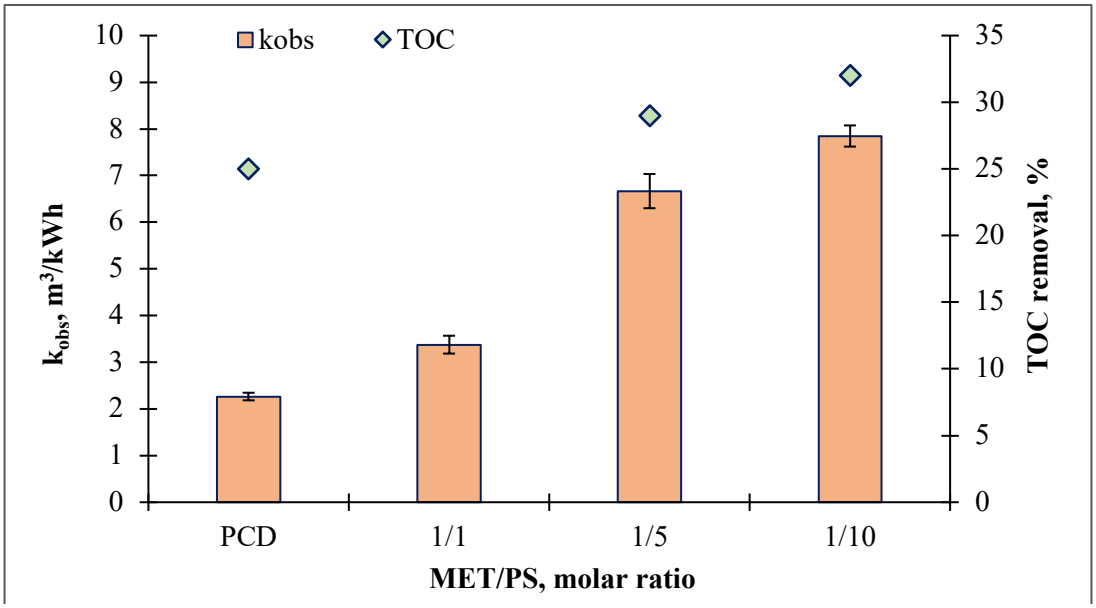

Fig. 3. Effect of MET/PS molar ratio on the k_{obs} and TOC removal in MET oxidation by PCD and PCD/PS combination ($[MET]_0$ = 60.4 μM, PCD output power 9 W, t_{TOC} = 2 h)

Irrespective of the studied pharmaceutical compound, the addition of persulfate increased the degradation rate, and in the case of VAN and MET, an increase in the PS concentration led to a further improvement in the oxidation rate. For example, the addition of PS at a MET/PS molar ratio of 1/1 and 1/5 increased the observed reaction rate constant 1.5 and 3 times, respectively, compared to non-assisted PCD (Fig. 3). In the case of VAN, the use of the same molar ratios led to faster decomposition of the target compound by factors of 1.3 and 1.6, respectively (Fig. 2). Regarding the degradation of DEX in the PCD/PS system, the results showed no apparent dependence of the rate of degradation on the added dose of PS (Fig. 4).

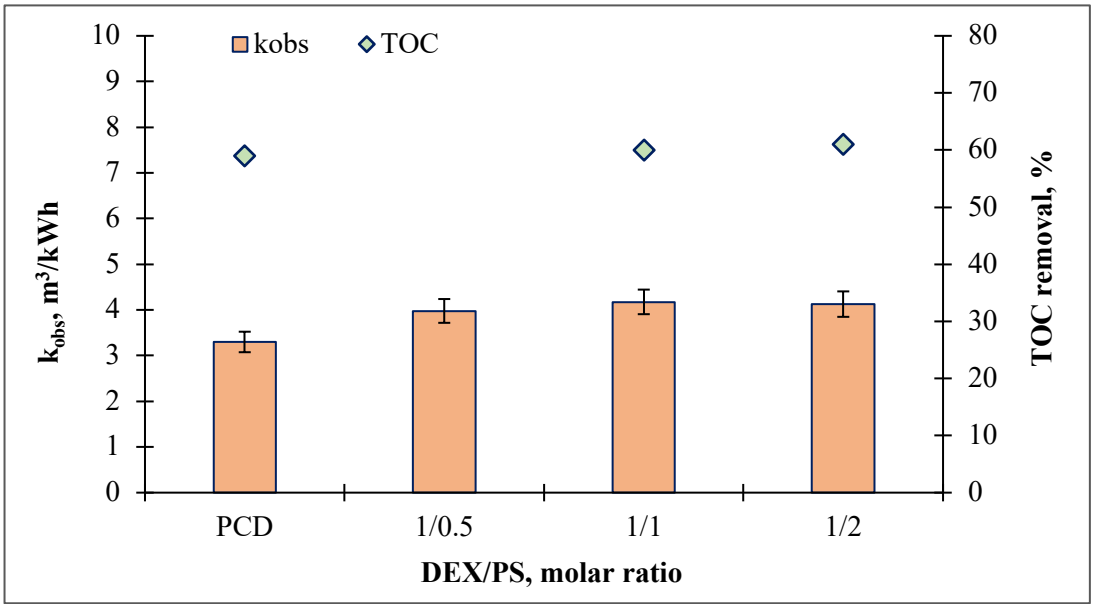

Fig. 4. Effect of DEX/PS molar ratio on the k_{obs} and TOC removal in DEX oxidation by PCD and PCD/PS combination ($[DEX]_0$ = 25.5 μM, PCD output power 32 W, t_{TOC} = 1 h)

The overall effectiveness of the treatment was assessed by the mineralization of the target pharmaceuticals, which was measured as the removal of TOC. Similar to the observed reaction rates, the TOC removal for all studied pharmaceuticals was higher in the PCD/PS combination compared to non-assisted PCD. These results clearly demonstrate the effectiveness of the combination of PCD with persulfate for the deep purification of water contaminated with pharmaceuticals. In general, the dose of added persulfate directly affected the pharmaceuticals oxidation performance in the combined PCD/PS system, accordingly, excessive concentrations exhibited a self-scavenging effect (Eqs. (4), (13)-(21)) [20] while low concentrations showed negligible improving effect.

$$SO_4^{\bullet -} + SO_4^{\bullet -} \rightarrow S_2O_8^{2-} \quad (13)$$

$$HO^{\bullet} + S_2O_8^{2-} \rightarrow S_2O_8^{\bullet -} + HO^- \quad (14)$$

$$SO_4^{\bullet -} + S_2O_8^{2-} \rightarrow SO_4^{2-} + S_2O_8^{\bullet -} \quad (15)$$

$$S_2O_8^{\bullet -} + 2e^- \rightarrow 2SO_4^{2-} \quad (16)$$

$$HO^{\bullet} + SO_4^{\bullet -} \rightarrow HSO_5^- \quad (17)$$

$$SO_4^{\bullet -} + HSO_5^- \rightarrow HSO_4^- + SO_5^{\bullet -} \quad (18)$$

$$HO^{\bullet} + HSO_5^- \rightarrow H_2O + SO_5^{\bullet -} \quad (20)$$

$$2SO_5^{\bullet -} \rightarrow S_2O_8^{2-} + O_2 \quad (21)$$

To evaluate the energy efficiency of PCD/PS combinations, energy yields at 90% conversion of the target pharmaceuticals (E_{90}) were calculated considering the energies applied by PCD treatment together with the cost of persulfate. The energy efficiency E_{90}, mmol/kWh, was calculated for 90% target compound degradation using Eq. (22):

$$E_{90} = \Delta C \cdot V/W \quad (22)$$

where ΔC – a decrease of target compound concentration, mmol/m^3; V – the volume of treated solution, m^3; W – energy consumption derived from the generator power output and the time of treatment, kWh.

The calculation results are shown in Table 2. The sodium persulfate cost of 1.5 EUR/kg is considered relevant including transportation and taxation based on average wholesale prices on market. The cost of the persulfate salt used was converted to its energy expense of 12 kWh/kg considering the average European non-household electric energy price of 0.125 EUR/kWh.

Table 2. Energy efficiencies for 90% target pharmaceuticals degradation in the studied processes ($[VAN]_0$ = 13.5 μM, PCD output power 8 W; $[MET]_0$ = 60.4 μM, PCD output power 9 W; $[DEX]_0$ = 25.5 μM, PCD output power 32 W)

Process	Pharmaceutical/oxidant, molar ratio	E_{90}, mmol/kWh		
		VAN	MET	DEX
PCD	-	160	54	33
PCD/PS	1/0.5	-	-	37
PCD/PS	1/1	127	64	37
PCD/PS	1/2	-	-	33
PCD/PS	1/5	50	45	-
PCD/PS	1/10	29	27	-

The results of the energy efficiency assessment showed that the addition of persulfate without a substantial improvement in the rate of oxidation had a negative effect on the E_{90} value. On the other hand, the use of moderate amounts of persulfate for MET and DEX demonstrated increased E_{90} values considerably dependent on the applied oxidant dose. For all pharmaceuticals studied, at the lowest studied PS concentrations, the combined PCD/PS system demonstrated energy efficiency close or even superior to non-assisted PCD process.

4. CONCLUSIONS

The combined PCD/PS oxidation proved effective in terms of degradation and mineralization of the studied aqueous pharmaceuticals belonging to different classes of drugs. Accordingly, for all studied pharmaceuticals, the addition of persulfate increased the degradation rate and the TOC removal compared to non-assisted PCD. In the case of VAN and MET, increasing the PS concentration resulted in a further improvement in the oxidation rate. Overall, the concentration of added PS directly affected the pharmaceuticals oxidation performance in the PCD/PS combination. Thus, the addition of excessive concentrations of persulfate resulted in a self-scavenging effect, while low concentrations of PS showed an insufficient efficiency-enhancing effect. The results of energy efficiency calculations indicated that using low to moderate concentrations of persulfate in the PCD/PS combination can improve energy efficiency compared to non-assisted PCD process. The results of this study contribute to the potential application of the combined PCD/PS process for efficient oxidation of aqueous pharmaceuticals.

ACKNOWLEDGMENTS

This work was supported by the Institutional Development Program of Tallinn University of Technology for 2016-2022, project 2014-2020.4.01.16-0032 from EU Regional Development Fund. The authors would like to thank Dr. Balpreet Kaur and Dr. Liina Onga for their assistance with the experiments.

REFERENCES

1. Puri, M, Gandhi, K & Kumar, MS 2023, "Emerging environmental contaminants: A global perspective on policies and regulations", *J. Environ. Manage.*, vol. 332, p. 117344.
2. Wang, J & Wang, S 2020, "Reactive species in advanced oxidation processes: Formation, identification and reaction mechanism", *Chem. Eng. J.*, vol. 401, p. 126158.
3. Ma, D, Yi, H, Lai, C, Liu, X, Huo, X, An, Z, Li, L, Fu, Y, Li, B, Zhang, M, Qin, L, Liu, S & Yang, L 2021, "Critical review of advanced oxidation processes in organic wastewater treatment", *Chemosphere*, vol. 275, p. 130104.
4. Ajo, P, Kornev, I & Preis, S 2017, "Pulsed corona discharge induced hydroxyl radical transfer through the gas-liquid interface", *Sci. Rep.*, vol. 7, pp. 1-6.
5. Aziz, KHH, Miessner, H, Mahyar, A, Mueller, S, Moeller, D, Mustafa, F & Omer, KM 2021, "Degradation of perfluorosurfactant in aqueous solution using non-thermal plasma generated by nano-second pulse corona discharge reactor", *Arab. J. Chem.*, vol. 14, p. 103366.
6. Ono, R & Oda, T 2003, "Dynamics of ozone and OH radicals generated by pulsed corona discharge in humid-air flow reactor measured by laser spectroscopy", *J. Appl. Phys.*, vol. 93, pp. 5876-5882.
7. Shang, K, Li, W, Wang, X, Lu, N, Jiang, N, Li, J & Wu, Y 2019, "Degradation of p-nitrophenol by DBD plasma/Fe^{2+}/persulfate oxidation process", *Sep. Purif. Technol.*, vol. 218, pp. 106-112.
8. Wang, Q, Zhang, A, Li, P, Héroux, P, Zhang, H, Yu, X & Liu, Y 2021, "Degradation of aqueous atrazine using persulfate activated by electrochemical plasma coupling with microbubbles: removal mechanisms and potential applications", *J. Hazard. Mater.*, vol. 403, p. 124087.
9. Ushani, U, Lu, X, Wang, J, Zhang, Z, Dai, J, Tan, Y, Wang, S, Li, W, Niu, C, Cai, T, Wang, N & Zhen, G 2020, "Sulfate radicals-based advanced oxidation technology in various environmental remediation: A state-of-the–art review", *Chem. Eng. J.*, vol. 402, p. 126232.
10. Duan, X, Yang, S, Wacławek, S, Fang, G, Xiao, R & Dionysiou, DD 2020, "Limitations and prospects of sulfate-radical based advanced oxidation processes", *J. Environ. Chem. Eng.*, vol. 8, p. 103849.
11. Gotvajn, AŽ, Rozman, U, Antončič, T, Urbanc, T, Vrabel, M & Derco, J 2021, "Fe^{2+} and UV catalytically enhanced ozonation of selected environmentally persistent antibiotics", *Processes*, vol. 9, pp. 1-17.
12. Okano, A, Isley, NA & Boger DL 2017, "Peripheral modifications of [Ψ[CH_2NH]Tpg4]vancomycin with added synergistic mechanisms of action provide durable and potent antibiotics", *Proc. Natl. Acad. Sci. USA*, vol. 114, pp. E5052-E5061.
13. Lindim, C, van Gils, J, Georgieva, D, Mekenyan, O & Cousins, IT 2016, "Evaluation of human pharmaceutical emissions and concentrations in Swedish river basins", *Sci. Total Environ.*, vol. 572, pp. 508-519.
14. Niemuth, NJ & Klaper, RD 2015, "Emerging wastewater contaminant metformin causes intersex and reduced fecundity in fish", *Chemosphere*, vol. 135, pp. 38-45.
15. Noreen, S, Maqbool, I & Madni, A 2021, "Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic", *Eur. J. Pharmacol.*, vol. 894, p. 173854.

16. Jia, A, Wu, SM, Daniels, KD & Synder, SA 2016, "Balancing the budget: accounting for glucocorticoid bioactivity and fate during water treatment", *Environ. Sci. Technol.*, vol. 50, pp. 2870-2880.
17. Kornev, I, Osokin, G, Galanov, A, Yavorovskiy, N & Preis, S 2013, "Formation of nitrite- and nitrate-ions in aqueous solutions treated with pulsed electric discharges", *Ozone Sci. Eng.*, vol. 35, pp. 22-30.
18. Dulova, N, Kattel, E, Kaur, B & Trapido, M 2020, "UV-induced persulfate oxidation of organic micropollutants in water matrices", *Ozone Sci. Eng.*, vol. 42, pp. 13-23.
19. Liu, Z, Guo, W, Han, X, Li, X, Zhang, K & Qiao, Z 2016, "In situ remediation of ortho-nitrochlorobenzene in soil by dual oxidants (hydrogen peroxide/persulfate)", *Environ. Sci. Pollut. Res.*, vol. 23, pp. 19707-19712.
20. Wang, S & Zhou, N 2016, "Removal of carbamazepine from aqueous solution using sono-activated persulfate process", *Ultrason. Sonochem.*, vol. 29, pp. 156-162.