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BDD-persulfate-based anodic oxidation process for progestin degradation: Optimization of conditions, eco-compatibility tests, and cost evaluation

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ABSTRACT

Considering the increasing presence of the hormones levonorgestrel (LNG) and gestodene (GES) in wastewater, the limited effectiveness of conventional treatment methods, and the demand for advanced complementary processes, our study aimed to optimize an anodic oxidation treatment with a focus on low specific energy consumption (SEC) and costs. An electrochemical system coupled to a boron-doped diamond anode (BDD) was continuously used to treat synthetic and real pharmaceutical wastewater from contraceptive production. The central design composite and response surface methodology were the tools employed for optimization. The lowest SEC was obtained as a response to the main process variables: current density, initial pH, and the concentration of the support electrolyte ($[Na_2S_2O_8]$). The optimal condition ($[Na_2S_2O_8]_0 = 0.07$ mol L^{-1}; $[LNG]_{0,RPW} = 1.02 \pm 0.05$ mg L^{-1} and $[GES]_{0,RPW} = 1.05 \pm 0.05$ mg L^{-1}; $j = 37.5$ mA cm^{-2}; pH = 6.75) was established considering an SEC $\leq 3.6 \pm 0.8$ kWh g^{-1} and progestins removal $\geq 70\%$, which was the experimental condition used to evaluate acute toxicity to *Daphnia similis* and the effect on estrogenic activity removal using the YES assay. Notably, our study evaluated, for the first time, a comparative investigation that highlights the substantial effect of support electrolytes over the eco-compatibility assessment of the anodic oxidation process investigated. The adaptability of the operation indicates the prospective suitability for the implementation of the process in wastewater treatment facilities in the pharmaceutical industry.

1. Introduction

The generation of pharmaceutical waste is associated with the consumption of medicines, drug consumption, contingent upon dosage, industrial production, incorrect discharge disposal, prescription, and metabolic processes. In the context of this study, the use of hormonal compounds in contraceptive methods assumes a paramount significance.

Commercially, oral contraceptives are available in two primary formulations: (i) combined oral contraceptives (COC), composed of estrogen and progestin, and (ii) emergency contraceptives (EC), composed only of progestin. In the first category, hormone dosages usually range from 0.03 to 3 mg of estrogen and 0.075–2.0 mg of progestin. For ECs, the progestin dose does not exceed 1.50 mg. In general, ethinylestradiol (EE2) serves as the estrogenic component, while progestins such as levonorgestrel (LNG) and gestodene (GES) are commonly employed. EC,

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List of abbreviations: ^{60}Co, Cobalt-60 radioactive isotope; AO, Anodic oxidation; AOP, Advanced oxidation processes; BDD, Boron doped diamond; BOD, Biochemical oxygen demand; CCD, Central composite design; COC, Combined oral contraceptive; COD, Chemical oxygen demand; CPRG, Chlorophenol red-β-D-galactopyranoside; DSA, Dimensionally stable anode; E2, 17β-estradiol; EAOP, Electrochemical advanced oxidation processes; EBI, Electron beam irradiation; EC, Emergency contraceptives; EC50, Effective concentration; EE2, Ethinylestradiol; EP, Electron-persulfate; GES, Gestodene; HER, Human estrogen receptor; IC50, Inhibitory concentration; LC-TOF-MS/MS, Liquid chromatography/ time-of-flight mass spectrometry; LNG, Levonorgestrel; LOD, Limit of detection; LOQ, Limit of quantification; MeOH, Methanol; NTU, Nephelometric turbidity unit; PS, Persulfate; PVC, Polyvinyl chloride; RPW, Real pharmaceutical wastewater; RSM, Response surface methodology; SEC, Specific energy consumption; SHE, Standard hydrogen electrode; SMWW, Standard Methods for the Examination of Water and Wastewater; SPE, Solid-phase extraction; TU, Toxicity unity; UFLC, Ultra-fast liquid chromatography; UV-C, Ultraviolet radiation 200–290 nm; YES, Yeast estrogen assay".

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often called the "morning-after pill," contains LNG exclusively" [19,28].

Given the substantial consumption of oral contraceptives in Brazil, estimated at 29.7 million units according to UN statistics in 2019, and the rates of excretion through urine (EE2: ~53%; LNG: ~77%; and GES: ~10%) [18,4], the presence of levonorgestrel and gestodene in Brazilian aquatic environments is anticipated [20], as also observed in Australia [18], China [38], Slovenia [12], Canada [16] and France [35].

Advanced Oxidation Processes (AOPs) are based on the generation of highly reactive oxidant species such as hydroxyl ($HO^{\bullet}$) or sulfate ($SO_4^{\bullet-}$) radicals, which can attack various organic and inorganic compounds, including aromatic, polyphenols, and halogenated compounds. Different processes have been applied to degrade the hormones LNG and GES, including ozonation [37], ionizing sources such as EBI and ^{60}Co [8], photocatalysis/UV-C [26], photocatalysis/persulfate [24], electrochemical degradation with graphite-PVC electrode [23], anodic oxidation using DSA electrodes [7].

AOPs based on the production of sulfate radical ($SO_4^{\bullet-}$) for the mineralization of organic contaminants are attracting interest owing to the high standard redox potential of this radical ($E^0 = 2.5–3.1$ V vs SHE), which is close to that of $HO^{\bullet}$ ($E^0 = 2.80$ V vs SHE) [21,9]. The reaction rate constants of sulfate and hydroxyl radicals with target organic pollutants vary widely ($10^7–10^{10}$ L mol^{-1} s^{-1}) depending on the functional groups present [21,9]. In addition, the sulfate radical ($SO_4^{\bullet-}$) has some significant advantages in comparison to the hydroxyl radical ($HO^{\bullet}$): high selectivity, a half-life of 30–40 μs (for $HO^{\bullet}$, 20 ns), and flexibility of operation over a wide pH range [1].

Among the AOPs, electrochemical oxidation is a promising technique due to its versatility, efficient energy consumption, automation, and environmentally friendly processing, in addition to the in-situ electrogeneration of the strong oxidants [15,33,36]. The anodic oxidation (AO) process is the most popular electrochemical AOP. In the process, organic compounds are oxidized/mineralized by hydroxyl radicals generated by water discharge onto the surface of an appropriate anode (M) having high O_2-evolution overpotential (Eqs. 1 and 2) [6].

$$H_2O + M \rightarrow M(^{\bullet}OH) + H^+ + e^- \quad (1)$$

$$M(^{\bullet}OH) \rightarrow M + \tfrac{1}{2}O_2 + H^+ + e^- \quad (2)$$

The BDD anode has outstanding characteristics for the electro-oxidation of organic pollutants due to its large potential window, high oxygen evolution over-potential, and applicability in very aggressive media owing to its inert surface with low surface adsorption properties and corrosion resistance. In addition, the electro-persulfate (EP) process has received notable consideration within electrochemical advanced oxidation processes (EAOPs). In the EP process, sulfate radicals are generated through the electrochemical activation of persulfate (Eqs. 3 and 4) [13].

$$SO_4^{2-} \rightarrow SO_4^{\bullet-} + e^- \quad (3)$$

$$S_2O_8^{2-} + e^- \rightarrow SO_4^{\bullet-} + SO_4^{2-} \quad (4)$$

Specifically, the activation of persulfate on BDD electrodes is considered one of the most efficient, versatile, and least polluting routes, in addition to the synergistic electro generation of $HO^{\bullet}$ radicals. Once adsorbed on the surface of the BDD electrode, persulfate (PS) can be converted by anodic discharge to the highly reactive PS* transition state. In this process, the sp^2 graphitic carbon of the BDD anode acts as an active site (C-O) for the electrochemical activation of adsorbed PS species to PS* (Eq. 5), which in turn can oxidize organic contaminant molecules via a non-radical route. In this process, the instability of these species allows for the occurrence of non-radical oxidative processes involving the target pollutant, generating intermediate degradation products (Eq. 6), as well as facilitating the water dissociation reaction on the BDD surface [10,40,9].

$$BDD + PS \rightarrow BDD(PS^*) \quad (5)$$

$$R + BDD(PS^*) \rightarrow \text{by-products} \quad (6)$$

In this work, persulfate radicals were electrogenerated on the BDD anode through anodic oxidation for the degradation of LNG and GES degradation in synthetic and real pharmaceutical wastewater. A central composite design was applied to stablish the lowest specific energy consumption (SEC) and maximum progestin removal from the degradation of the target contaminants in a mixture (LNG+GES). With regard to the study, the following scientific questions were considered: (i) which electrochemical process variables have the greatest effect on SEC? (ii) what are the most promising experimental conditions for operating the electrochemical systems studied? (iii) what are the effects of the by-products of the anodic oxidation of progestins on the eco-compatibility of the treated solutions? (iv) which anodic electrochemical system results in the lowest specific cost and best performance?

2. Materials and methods

2.1. Reagents and real pharmaceutical wastewater

Levonorgestrel (LNG, $C_{21}H_{28}O_2$, ≥ 98.0%) and gestodene (GES, $C_{21}H_{26}O_2$, ≥ 98.0%) were purchased from Zhejiang Xianju Pharmaceutical Co. Ltd. LNG and GES were used as standards in the chromatographic analysis and all experiments. HPLC-grade methanol (MeOH), 17β-estradiol (E2) ($C_{18}H_{24}O_2$, ≥ 98%, CAS 50–28–2) were purchased from Sigma-Aldrich and used without further purification. Chlorophenol red-βD-galactopyranoside (CPRG) and sodium persulfate pentahydrate ($Na_2S_2O_8 \cdot 5\,H_2O$, ≥ 99.0%) were purchased from Merck. Real pharmaceutical wastewater (RPW) from contraceptive production was sampled in a pharmaceutical industry in Goiânia (Brazil), prior to biological treatment. The sample was collected, stored in a plastic drum, and kept at 20° C for later analysis (Table S1). Visual observations indicated that the RPW samples contained a considerable amount of suspended material (Fig. S1); thus, LNG and GES could be found in solution and associated with the suspended solids due to the low solubility of these compounds in water (GES = 8.12 mg L^{-1}, LNG = 2.05 mg L^{-1}) [7]. The concentrations of soluble LNG and GES were determined by LC-TOF-MS/MS (Fig. S2), for which the RPW samples were previously syringe-filtered with 0.22 μm membranes. Ultra-pure water with a resistivity of 18.2 MΩ cm^{-1}, generated in a Milli-Q® system (Millipore), was used to prepare the synthetic solutions.

2.1.1. Electrochemical reactor

A single-compartment electrochemical cell containing a boron-doped diamond (BDD) anode (Hunan Boromond EPT Co. Ltd. - Table S2) and a stainless-steel cathode was used. Both electrodes have an active area of 20 cm^2 and were separated by 13 mm by an acrylic separator arranged in parallel. The power supply (30 V/5 A MPS 300–5B MINIPA) was a constant current source. The work solutions (300 mL) were recirculated from a borosilicate glass reservoir into the electrochemical cell with a peristaltic pump (DM 500) at a continuous flow rate of 0.75 mL s^{-1}. The internal volume of the electrochemical cell was 36.4 mL, and all experiments were carried out using a space-time of 16 s in each passage (Fig. 1).

The operating conditions for all experiments are summarized in Table 1. The progestin solutions were sampled at 0, 2, 4, 6, 8, 10, 15, 20, 25, and 30 min for UFLC analysis. The sample volume was 900 μL, to which 100 μL of methanol was added to stop further reactions [22].

2.2. Experimental design

A central composite experimental design (CCD) was applied to evaluate the effect of three independent variables: $[Na_2S_2O_8]_0$ (mol L^{-1}), current density j (mA cm^2), and initial pH on the specific energy consumption (SEC, kWh g^{-1}) of the anodic oxidation process. Table S4 presents these parameters, converted into dimensionless values coded as

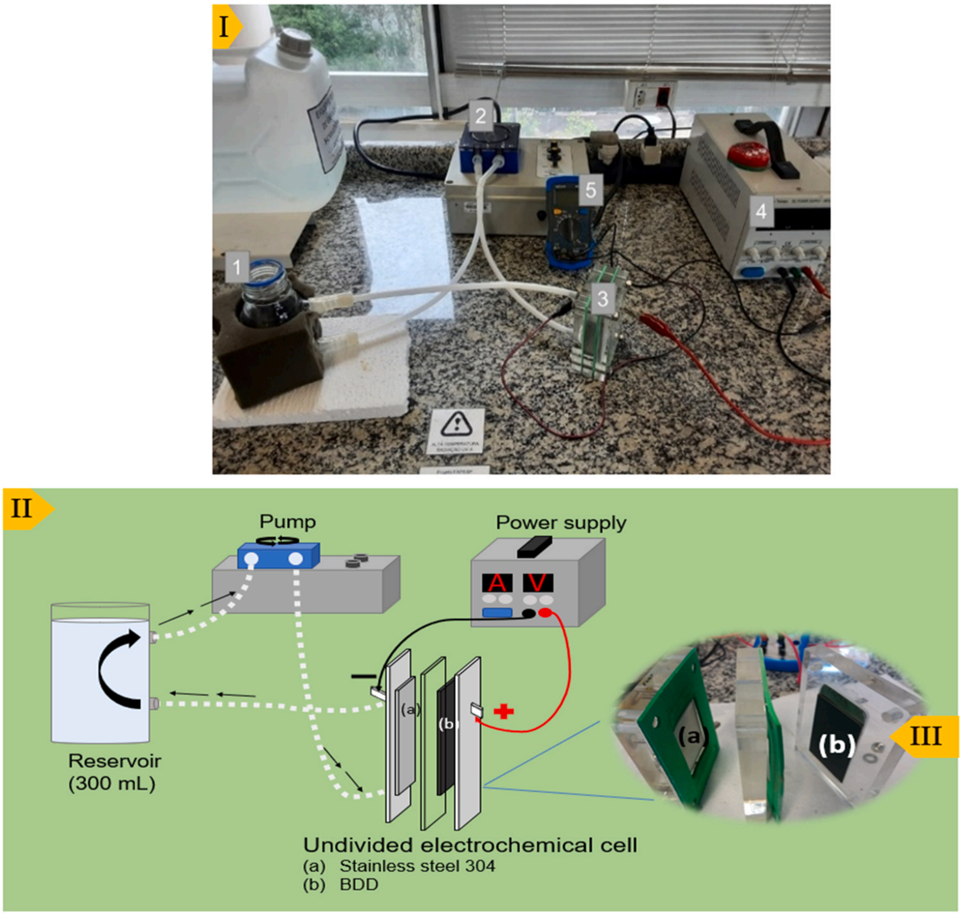


Fig. 1. (I) Electrochemical apparatus used for the degradation of progestins via anodic oxidation. (1) Reservoir; (2) Peristaltic pump; (3) Electrochemical cell; (4) Power supply; (5) Multimeter. (II) Schematic representation of the electrochemical apparatus, with (III) highlighting the open electrochemical cell. All experiments were carried out at room temperature (≤ 30°C).

Table 1
Central composite design matrix (2^3) with real and coded values and the responses relating to specific energy consumption (SEC) using the BDD-PS process for the degradation of levonorgestrel (LNG) and gestodene (GES) in the mixture. Electrolysis time: 10 min.

Run	Coded levels			Original variables			pH_{30}	Response	Removal efficiency (%)		k_{obs} (min^{-1})			
	X_1	X_2	X_3	$[Na_2S_2O_8]_0$ (mol L^{-1})	j (mA cm^{-2})	pH_0		SEC (kWh g^{-1})	LNG	GES	LNG	R^2	GES	R^2
1	−1	−1	−1	0.04	25.0	4.5	3.5	1.9	76.1	85.1	0.137	0.935	0.159	0.946
2	+1	−1	−1	0.10	25.0	4.5	2.4	3.4	42.4	41.9	0.078	0.837	0.074	0.883
3	−1	+1	−1	0.04	50.0	4.5	2.6	16.2	24.2	33.9	0.026	0.987	0.033	0.931
4	+1	+1	−1	0.10	50.0	4.5	2.0	21.8	22.8	35.4	0.029	0.965	0.046	0.972
5	−1	−1	+1	0.04	25.0	9.0	3.7	2.3	22.9	100.0	0.033	0.853	0.292	0.987
6	+1	−1	+1	0.01	25.0	9.0	2.9	15.1	14.4	19.8	0.022	0.846	0.031	0.883
7	−1	+1	+1	0.04	50.0	9.0	2.7	2.3	94.5	92.3	0.298	0.839	0.254	0.947
8	+1	+1	+1	0.10	50.0	9.0	3.0	7.7	64.6	49.4	0.122	0.931	0.062	0.933
9	−1.68	0	0	0.02	37.5	6.75	2.8	5.9	30.5	48.3	0.064	0.969	0.073	0.926
10	+1.68	0	0	0.12	37.5	6.75	2.1	18.5	24.2	10.1	0.029	0.918	0.033	0.925
11	0	−1.68	0	0.07	16.48	6.75	2.6	3.6	22.4	34.5	0.032	0.979	0.039	0.972
12	0	+1.68	0	0.07	58.53	6.75	2.2	20.4	10.1	37.7	0.017	0.780	0.083	0.989
13	0	0	−1.68	0.07	37.5	2.97	2.3	7.1	15.4	24.3	0.072	0.984	0.042	0.945
14	0	0	+1.68	0.07	37.5	10.53	2.6	6.9	33.2	51.5	0.059	0.951	0.078	0.995
15	0	0	0	0.07	37.5	6.75	2.4	4.9	64.5	57.7	0.093	0.989	0.379	0.813
16	0	0	0	0.07	37.5	6.75	2.5	3.7	78.3	89.9	0.146	0.975	0.164	0.863
17	0	0	0	0.07	37.5	6.75	2.9	2.8	91.3	92.3	0.185	0.892	0.187	0.859
18	0	0	0	0.07	37.5	6.75	3.2	3.4	78.9	95.8	0.125	0.886	0.320	0.978
19	0	0	0	0.07	37.5	6.75	2.9	3.9	77.8	92.1	0.159	0.987	0.367	0.965
20	0	0	0	0.07	37.5	6.75	2.2	2.7	72.8	97.1	0.088	0.838	0.372	0.814

X_1, X_2, and X_3 at five levels (−1.68, −1, 0, +1, and +1.68). The value levels for $[Na_2S_2O_8]_0$ was selected based on previous studies [14], as well as for pH [25] and current density [7]. The pH values in Table S4 were initially adjusted with 0.01 mol L^{-1} NaOH or 0.01 mol L^{-1} H_2SO_4 solutions and checked at the end of each experiment.

The initial concentration of LNG and GES was not evaluated as an independent variable because, in a previous study using the DSA-Cl_2 system [7], the lowest specific energy consumption (~2.0 kWh g^{-1}) and high removals ≥70% were obtained when the hormones were employed at equal concentrations (~1.0 mg L^{-1}). Thus, for the present study with the BDD-PS, the initial concentrations of the progestins were $[LNG]_0 = 0.97 \pm 0.14$ mg L^{-1} and $[GES]_0 = 1.06 \pm 0.30$ mg L^{-1}.

To compare the electrochemical systems applied to the degradation of the progestin mixture, the same parameters presented by [7]) were determined (F-value, p-value, and R^2). The response surface methodology (RSM) was applied to identify the optimum operating conditions for the degradation of LNG and GES, to minimize the SEC (Eq. S1).

2.3. Analytical methods

The identification and quantification of progestins in real pharmaceutical wastewater was carried out using a time-of-flight mass spectrometer (LC-TOF-MS/MS, Shimadzu). For this purpose, the sample was nebulized and ionized at atmospheric pressure with an electrospray probe (ESI) in positive and negative mode, operated at 4.5 kV. The dissolution curve line interface (CDL) was operated at 200 °C. Fragmentation of the molecules in tandem mass mode (MS/MS) was carried out by collision-induced dissociation with N_2 (> 99.99%), with collision-induced dissociation energy (CID) of 50%. The chromatograms and mass spectra for the hormones LNG and GES in RPW are shown in Fig. S2.

The concentration of GES and LNG was monitored by ultra-fast liquid chromatography (UFLC) using a Shimadzu equipment (LC 20 AD) equipped with a UV–visible detector (SPD 20A) and a C18 column (ACE, 250 mm × 4.60 mm, 5 μm); only for the identification of hormones in the real pharmaceutical wastewater from the contraceptive production process, it was necessary to use mass spectrometry (LC-TOF-MS/MS). An isocratic method was applied using 70% methanol and 30% water containing 1% v/v acetic acid as the mobile phase [32]. Both hormones were detected at 244 nm. The sample injection volume, oven temperature, and flow rate were 20 μL, 40 °C, and 1.0 mL min^{-1}, respectively. Under these conditions, the retention times of GES and LNG were 8.0 and 10.0 min, respectively. Due to the low solubility of LNG (2.05 mg L^{-1} in H_2O), stock solutions (10 mg L^{-1}) were prepared in methanol and used to prepare the standard. Two calibration curves were obtained by diluting the stock solutions to obtain LNG and GES standards from 0.05 to 10.0 mg L^{-1}. Table S3 presents the validation parameters of the calibration curves.

2.3.1. SPE – solid phase extraction

The synthetic samples targeted for estrogenic activity assays and the real pharmaceutical wastewater from the contraceptive production process were concentrated using C18 cartridges (SPE Strata 200 mg/3 mL). The SPE protocol consisted of the following steps: (i) conditioning the cartridges with 10 mL of methanol and 10 mL of pure water; (ii) percolation of 10 mL of the progestin samples at 4 mL min^{-1}; (iii) cleaning with 10 mL of an aqueous methanol solution (2% v/v); and (iv) elution of the analytes with 2 mL of methanol. The recoveries of the LNG and GES extraction were (91.60 ± 0.04)% and (84.90 ± 2.47)%, respectively (Table S3).

2.4. Eco-compatibility tests

2.4.1. Acute ecotoxicity (Daphnia similis)

The ABNT NBR 12713 standard [3] presents the detailed methodology for carrying out acute toxicity tests using test organisms of the *Daphnia* genus. *Daphnias similis* were cultivated at the Laboratory of Biological and Environmental Assays (Nuclear and Energy Research Institute-IPEN-CNEN/SP, São Paulo, Brazil). The assays sought to evaluate the effects of progestins under the following conditions: (A) progestins mixture (LNG+GES) without electrolytic processing and in the absence of $Na_2S_2O_8$; (B) progestin mixture (LNG+GES) without electrolytic processing in the presence of $Na_2S_2O_8$; (C) $Na_2S_2O_8$ solution without electrolytic processing; (D) $Na_2S_2O_8$ solution with electrolytic processing; and (E) the progestin mixture (LNG+GES) with electrolytic processing in the presence of $Na_2S_2O_8$. To this end, neonates between 6 h and 24 h were exposed to progestin solutions at concentrations of 6.25%, 12.5%, 25%, 50%, 75%, and 100%, diluted in culture water (Fig. S3). After the adaptation period in the incubator, five test organisms were added to each test tube. The total exposure was 48 h, and the test was static, i.e., without feeding the micro crustaceans. The pH of the samples was adjusted to 7.0 [3]. Acute ecotoxicity was obtained visually as a function of the mobility of the test organisms, which is expressed in toxicity units (TU = 100/EC50%) and corresponds to the average effect concentrations that promoted 50% immobility of the exposed living organisms (EC50%-48 h, expressed in % v/v).

2.4.2. Yeast estrogen assay (YES)

The YES methodology with modifications [2] was applied to assess the estrogenicity of LNG and GES solutions before and after electrolysis. YES, created by Routledge and Sumpter [30], is based on the application of *Saccharomyces cerevisiae* genetically modified with a human estrogen receptor (hER). The tests were performed in collaboration with the Laboratory of Sanitary Engineering (LES) team at Rio de Janeiro State University (UERJ, under the coordination of Prof. Daniele M. Bila.

Before the test, the samples were concentrated in C18 cartridges (SPE Strata 200 mg/3 mL), following the procedure described in Section 2.3.1. The bioassay was carried out in 96-well microplates by diluting the extracts in ethanol, thus obtaining standards. The hormone 17β-estradiol (E2) (acetonitrile: water of 55:45 v/v) was used as a positive control to obtain a standard curve in the range of 1.33–2724 ng L^{-1}, while ethanol was used as a negative control (NC) (Fig. S4).

In the test plate, 10 μL of each progestin standard and 200 μL of culture medium containing yeast and chromogenic substrate CPRG (chlorophenol red-β-D-galactopyranoside) were added and evaporated. After 72 h of incubation at 30 °C, the plate was analyzed on the VersaMax (Molecular Devices®) at wavelengths of 575 nm (for colour) and 620 nm (for turbidity).

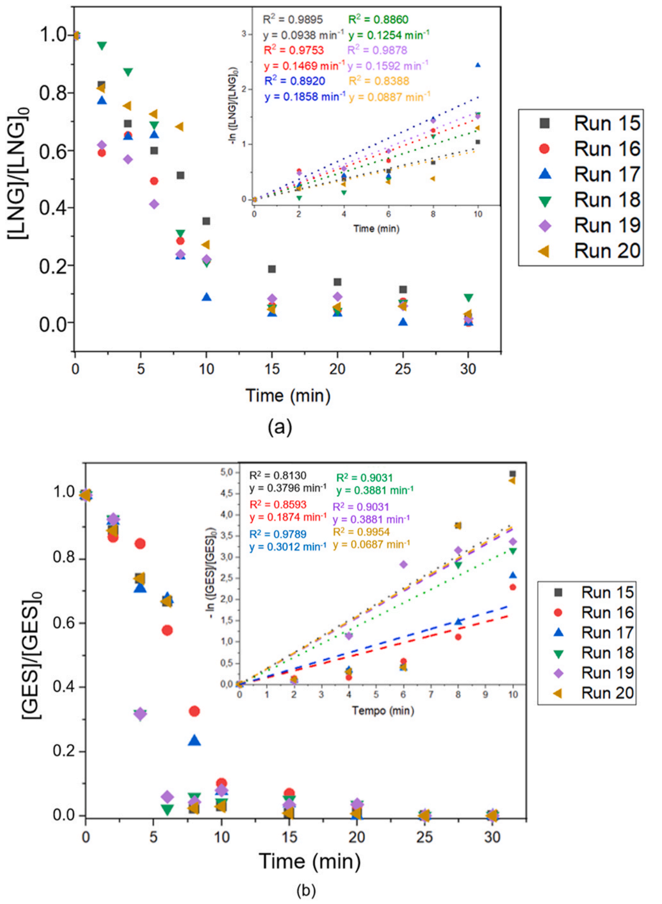
To obtain the dose-response curves E2 and the samples, the absorbance values were corrected to discount the turbidity effect caused by yeast using Origin 2020 software (Eq. S2). Another parameter obtained from the estrogenicity dose-response curves was the effect concentration of the hormones, which allowed 50% of the CPRG response (IC50).

3. Results and discussion

3.1. Optimization of operational parameters

Table 1 shows the CCD matrix applied for the statistical analysis, including the SEC response surface function and the removal percentages for both progestins. The specific degradation rates (k_{obs}, min^{-1}) and high coefficients of determination ($R^2 \geq 0.781$) suggest that the electrolytic degradation of LNG and GES followed a pseudo-first-order behavior. It was expected that the use of high variable levels, especially current density, provided a high SEC; however, among the 20 experiments managed in the BDD-PS system, run 4 had the highest SEC, followed by run 12 and run 10, with 21.8, 20.4, and 18.5 kWh g^{-1}, respectively. In addition to achieving the highest SEC, run 4 ($[Na_2S_2O_8]_0$= 0.1 mol L^{-1}, j = 50 mA cm^{-2}, pH = 4.5) was the only condition that reached more than 80% of both progestin with 94.5 and 92.3% removal of LNG and GES, respectively. As with run 4 being operated at levels ($X_1 = +$, $X_2 = +$, and $X_3 = -1$), this evidence suggests interaction effects between the variables.

Fig. 2 shows the results of runs 15–20 carried out under the conditions of the central point of the CCD design (Table 1). The assays were performed under the following conditions: $[LNG]_0 = 0.97 \pm 0.14$ mg L^{-1} and $[GES]_0 = 1.06 \pm 0.30$ mg L^{-1}; current density: 37.5 mA cm^{-2}, $pH_0 = 6.75 \pm 0.24$ and $[Na_2S_2O_8]_0 = 0.07$ mol L^{-1}. In



(a)

(b)

Fig. 2. Relative concentrations of LNG (a) and GES (b) as a function of treatment time (BDD-PS system) and pseudo-first order kinetic fits of progestin degradation in 10 min of the experiment. Conditions: $[LNG]_0 = 0.97 \pm 0.14$ mg L^{-1} and $[GES]_0 = 1.06 \pm 0.30$ mg L^{-1}; current density: 37.5 mA cm^{-2}, $pH_0 = 6.75 \pm 0.24$ e $[Na_2S_2O_8]_0 = 0.07$ mol L^{-1}.

runs 15–20, the initial pH values were set at 6.75, and after 30 minutes of electrolysis, the average pH was 2.68 ± 0.38.

From these results, the progestins in the mixture were degraded in 30 minutes of electrolysis, reaching concentrations below their respective LOD and LOQ values (Table S3). Run 15–20 achieved average removals in 10 min of electrolysis of (77.3 ± 8.7)% and (87.5 ± 14.0)% for LNG and GES, respectively. For the specific removal rates, the decay of the concentrations of both hormones followed pseudo-first-order behavior during 10 min of reaction, with k_{obs} values of 0.133 ± 0.040 min^{-1} for LNG and 0.299 ± 0.100 min^{-1} for GES (Fig. 2).

Table S5 allowed us to obtain the quadratic equation that expresses the relationship between the response (SEC) and operating parameters (Eq. 7).

$$\mathrm{SEC}(\mathrm{kWh\ g^{-1}}) = 3.630 - 1.188X_1 + 3.921X_2 + 3.404X_3 + 0.796X_1^2 + 2.564X_2^2 + 2.635X_3^2 + 1.387X_1X_3 - 5.012X_2X_3 \quad (7)$$

The coefficient of determination obtained indicates that 93.2% of the data fit the model; the significance of the model is at the 95% confidence level. The effect of more than two independent variables is analyzed using ANOVA, for which the significance level (α) is 5% ($p < 0.05$) (Table S6). If the computed F value exceeds the critical table value, the terms are deemed to exhibit a statistically significant difference according to the F-test within the framework of the null hypothesis. If the determined p-value derived from ANOVA is less than the predetermined α-value, signifying statistical significance, it is affirmed that the outcome is noteworthy. Conversely, when the p-value exceeds the α-value, it is posited that the null hypothesis is accepted, thereby indicating a lack of significant disparity in the results [17].

As can be seen from the results (Table S6), the F-value of the model (1250.53) was higher than the tabulated F-value [$F_{0.05,\ df(n-(df+1))} = 4.77$] and the p-value was very low (<0.0001). The low p-value (Prob > F) indicates that the terms had high importance on the model. The error caused by the inconsistency of the mathematical form of the model is called the model inconsistency (lack of fit). The difference (residue) between the experimental data and the predicted values depends not only on the pure experimental error but also on the lack of fit. The significant lack of fit F-value of 16.37 implies that some experimental variables were not contemplate through the model, despite its strong data correlation and model prediction (Fig. S5a). With regard to the residuals (Fig. S5b), the symmetrical distribution and the tendency to cluster close to zero error confirm the quality of the model obtained.

According to Eq.7 and the F values (Table S6), the impact of the operating parameters on SEC for progestin removal follows the order: X_2 (j) > X_3 (pH_0) > X_1 ($[Na_2S_2O_8]_0$. Although current density showed a positive effect on SEC in BDD-PS for LNG and GES removal, it was observed that the use of high current density did not improve SEC or hormone removal due to the occurrence of the oxygen evolution side reaction [5].

The response surface (Fig. 3) was constructed from the validation of the model using analysis of variance. Fig. 3**b** shows a saddle point profile for the variation in specific energy consumption as a function of the variables X_1 ($[Na_2S_2O_8]_0$) and X_3 (pH). The response surface shows the region of lowest energy consumption, where the central point with SEC < 4.0 kWh g^{-1} is located.

Among the operating parameters evaluated, current density had the most influence on the response, in which an increase in j leads to an increase in SEC. In contrast, this variable did not affect the percentage of progestin removal, as Nashat et al. [25] observed. The authors evaluated the efficiency of the BDD-PS system in terms of sulfamethazine degradation (SMD) using a CCD experimental design for the variables pH, $[Na_2S_2O_8]_0$ and j at five levels [25]. The mathematical model obtained made it possible to determine the importance of the variables (PS concentration > current density > pH). Regarding the effect of current density, the authors also identified that increasing this parameter did not contribute to removal efficiency despite the increase in the generation of oxidative species of interest. However, increasing the current density contributes to parallel reactions, such as the electrochemical oxygen transfer reaction, which is the main pathway that limits the generation of radicals on the electrode surface. In addition, Nashat et al. [25] found a maximum SMD removal efficiency for low values of current density (21.43 mA cm^{-2}) and pH (4.0).

The degradation of LNG and GES by the electrogenerated sulfate and hydroxyl radicals can occur on the anode surface via (i) direct oxidation by physically adsorbed $HO^{\bullet}$ radicals on the BDD surface (Eq. 8); (ii) indirect oxidation mediated by persulfate activation on the BDD anode surface (Eqs. 5 and 6); (iii) additional sulfate radicals produced by the reaction of persulfate with $HO^{\bullet}$ radicals on the anode surface (Eq. 9) [10,25,5].

$$\text{progestins} + \mathrm{BDD}(^{\bullet}\mathrm{OH}) \rightarrow \mathrm{BDD} + \text{by-products} + \mathrm{H}^{+} + \mathrm{e}^{-} \quad (8)$$

$$\mathrm{S_2O_8^{2-}} + \mathrm{HO}^{\bullet} \rightarrow \mathrm{HSO_4^{-}} + \mathrm{SO_4^{\bullet-}} + 0{,}5\ \mathrm{O_2}\quad k = 1.2 \times 10^{7}\ \mathrm{L\ mol^{-1}\ s^{-1}} \quad (9)$$

The reactions given by Eqs. 5 to 8 occur regularly in an electrochemical process with BDD anodes and persulfate as the supporting electrolyte [10,25,5].

In the BDD-PS system, pH was one of the variables evaluated, so this parameter was measured after each test (Table 1). The data shows that, in all the conditions evaluated, the final pH (after 30 min of electrolysis) corresponds to an acidic environment (2.0–3.5). The acidic pH of the treated solutions is related to the intrinsic reactions of the BDD electrode responsible for the evolution of O_2 (Eqs. 1 and 2), decomposing water

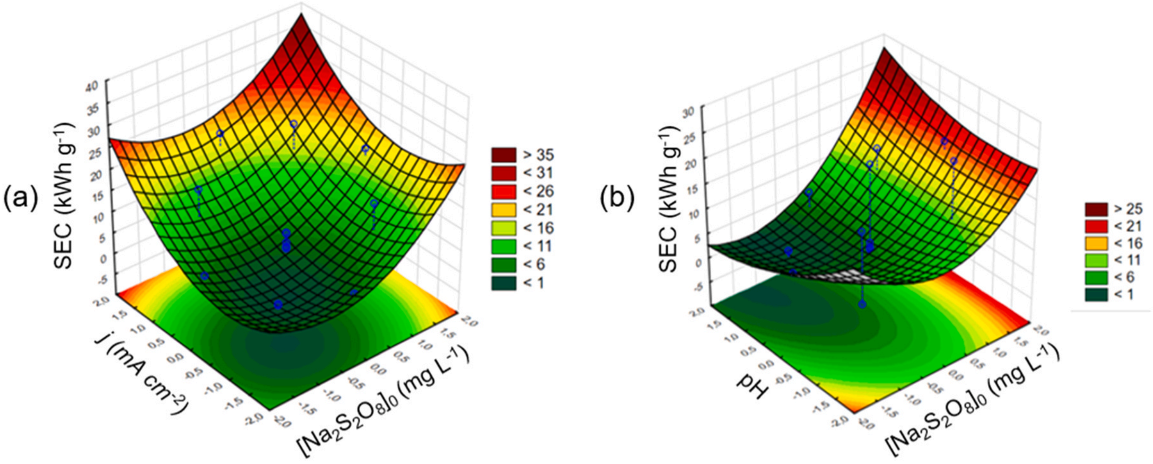


Fig. 3. Response surface for specific energy consumption (SEC) as a function of the independent variables.

into physisorbed HO● radicals and H^+, and also to the possible formation of organic acids as degradation by-products resulting from the oxidation of LNG and GES, as observed for the BDD system and other emerging contaminants [31,34].

About the initial pH, progestins degradation increased at neutral pH. At ($pH < 4.5$) or ($pH > 9.0$), the average removals of LNG and GES were 44.1% and 62.5%, respectively. On the other hand, degradation efficiency at neutral pH was over 70%. Under basic conditions, the electrophilic attack of hydroxyl radicals is favored [39]; their generation is also promoted by an increase in the concentration of hydroxide anions from their reaction with sulfate radicals, which in some cases increases the removal of the target pollutant (Eq. 10) [21,25].

$$SO_4^{\bullet -} + HO^- \rightarrow HO^\bullet + SO_4^{2-} \qquad (10)$$

3.2. Optimum condition applied in RPW

Based on the CCD-RSM analysis, it was possible to determine the optimal point of the experimental design, which presents critical values within the experimental domain (Table 2). Furthermore, as a response, an SEC of 1.35 kWh g^{-1} is estimated in the optimal condition.

In order to compare the DSA-Cl_2 [7] and BDD-PS systems, the conditions of the central point were chosen as the most convenient condition due to the similarity of the values of the independent variables (current density and support electrolyte concentration). Thus, the real pharmaceutical wastewater sample was subjected to anodic oxidation using the BDD-PS system.

Fig. 4 shows the concentration decay of the progestins LNG and GES in the RPW matrix over 30 min of electrolysis in the BDD-PS system and the corresponding pseudo-first-order kinetic profile. The electrolytic process mediated by PS and HO● radicals promoted removals of (58.6 ± 0.5)% and (80.3 ± 0.7)% of LNG and GES in the RPW, respectively. After 10 min of treatment, the continuation of the process allowed GES concentrations below the LOD ($\leq$ 0.06 mg L^{-1}). On the other hand, after 30 min of testing, the residual concentration of LNG was 0.08 mg L^{-1}, corresponding to 92.7% removal of the progestin.

The progestins LNG and GES showed pseudo-first-order degradation rates in real (Fig. 4) and synthetic water matrices (Fig. 2). For LNG, the k_{obs} in the mixture was 0.133 ± 0.200 min^{-1}, while in the pharmaceutical effluent, the kobs was 0.093±0.300 min^{-1}, i.e., 1.4 times lower. On the other hand, GES showed k_{obs} equal to 0.299 ± 0.100 min^{-1} in the synthetic solution and 0.350 ± 0.100 min^{-1} in the RPW, representing a 1.2-fold increase in its degradation rate when degraded in the real matrix. The results suggest a more pronounced matrix effect for the degradation of LNG, which is attributed to the presence of other substrates in the RPW. In addition, despite these differences in the observed kinetic constants of progestins for the treatment of RPW with BDD-PS, the percentage of removal of both LNG and GES was lower than that observed in synthetic solutions. It is worth noting that De Jesus et al. [8] evaluated the effect of the matrix on the radiolytic degradation of LNG and GES, observing a markedly distinct degradation behavior between LNG and GES, which was associated with differences in chemical structure.

The specific energy consumption obtained for the progestins in synthetic solutions in runs 15–20 ($SEC_{average} = 3.6 \pm 0.8$ kWh g^{-1}) were similar to the values obtained using RPW (2.4 ± 0.2 kWh g^{-1}). This evidence indicates a satisfactory reproducibility of the BDD-PS system and emphasizes the applicability of the process for the treatment of a real matrix.

Table 2
Optimum values for $[Na_2S_2O_8]_0$, j (mA cm^{-2}), and pH.

Variable	Estimated values
$[Na_2S_2O_8]_0$ (mg L^{-1})	0.04
j (mA cm^{-2})	33.9
pH	8.0

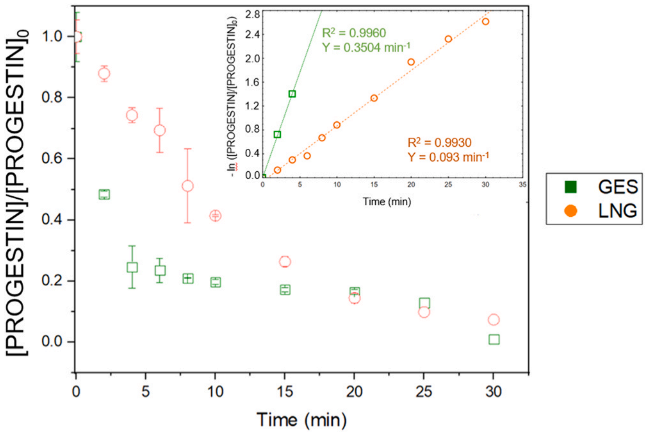


Fig. 4. Evolution of the relative concentrations of LNG and GES in the real pharmaceutical wastewater as a function of treatment time (BDD-PS system) and pseudo-first-order kinetic fits of progestins degradation (insert). Conditions: $[Na_2S_2O_8]_0$ = 0.07 mol L^{-1}; $[LNG]_{0,RPW}$ = 1.02±0.05 mg L^{-1} and $[GES]_{0,RPW}$ = 1.05±0.05 mg L^{-1}; j = 37.5 mA cm^{-2}; pH = 6.75 and conductivity 15.88 mS m^{-1}. Error bars correspond to n=2 replicates.

3.3. Estrogenic activity removal

The effects of anodic oxidation conducted in the BDD-PS system on progestins degradation were investigated using in vitro estrogenic activity tests, as described in Section 2.4.2. The hormone 17β-estradiol (E2) was used as a standard to obtain a dose-response curve (Fig. S4).

As discussed in Section 3.2, the central point was the optimum condition chosen within the CCD experimental design. Thus, the solution obtained after anodic oxidation conducted in the BDD-PS system was evaluated via YES. The electrochemical treatment time for the biological tests was 30 min to ensure maximum removal of both progestins.

The initial estrogenicity of the progestin mixture showed an average value of 267.0 ± 13.5 E2-EQ ng L^{-1}. This value was five times higher than the EC50 of E2 (49.5 ng L^{-1}). Unlike what was previously observed for the DSA-Cl_2 system by the authors [7], the BDD-PS process promoted total removal of the estrogenic activity from the sample (≤ LOD 5.9–2.34 E2-EQ ng L^{-1}) after electrolysis of the LNG and GES mixture for 30 min (Fig. 5). Concerning the anodic oxidation of LNG and GES mediated by sulfate and $HO^{\bullet}$ radicals, this is the first time that estrogenic activity has been applied to investigate the effect of electrogenerated byproducts.

3.4. Investigation into the mobility of the *D. similis*

The ecotoxicological evaluation involving the motility of *D. similis* was carried out to examine the mixture of progestins and PS before and after the anodic oxidation process using the BDD-PS system (as illustrated in Fig. 6). The experimental parameters under consideration concern the central point conditions.

Based on these results, the main determinant of ecotoxicity in the samples tested is residual persulfate (sample B). This is substantiated by the 18-fold increase in the toxic unit observed after the introduction of the electrolyte in comparison to sample A. Notably, the average UT value of 53.2 ± 2.6 was consistently maintained under the other investigated conditions (samples D and E), meaning that anodic oxidation through $SO_4^{\bullet -}$ and $HO^{\bullet}$ radicals did not contribute to the significant increase in acute toxicity, sample B (UT = 46.3 ± 2.3) [29].

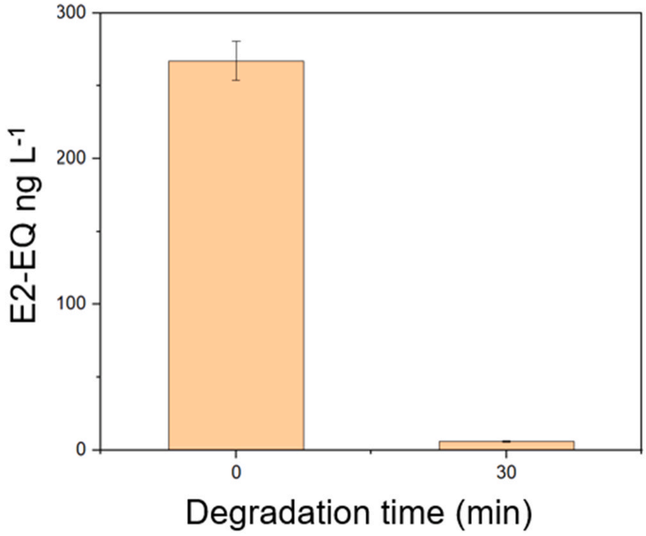


Fig. 5. Removal of estrogenic activity (E2-EQ) after 30 min of anodic oxidation mediated by hydroxyl and sulfate radicals (BDD-PS system) in a solution containing LNG and GES, according to the conditions of the central point. (pH_0 = 6.75 ± 0.24, $[PS]_0$ = 0.07 mol L^{-1} e j = 37.5 mA cm^{-2}). YES assays were carried out in duplicate.

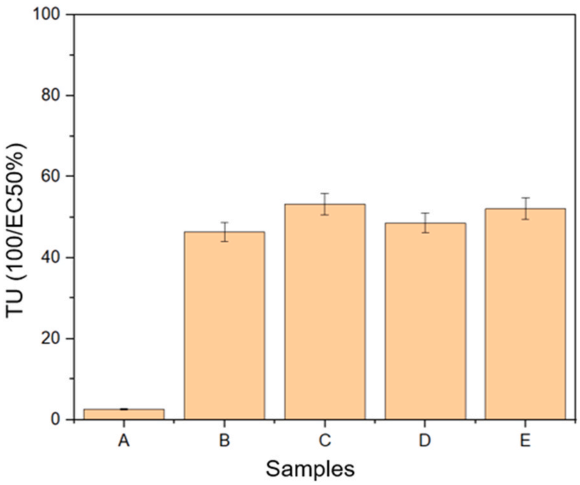


Fig. 6. Acute toxicity tests (in toxicity units, UT = 100/EC50%) for *D. similis* before and after electrochemical treatment using the BDD-PS system for the samples: (A) MIX 0' (without PS), (B) MIX 0' (with PS), (C) PS (without electrolysis); (D) PS (after electrolysis), (E) MIX 30' (with PS). Conditions: $[LNG]_0$ = 0.97 ± 0.14 mg L^{-1}; $[GES]_0$ = 1.06 ± 0.30 mg L^{-1}; j = 37.5 mA cm^{-2}; $[PS]_0$ = 0.07 mol L^{-1}.

3.5. Comparison: DSA-Cl_2 vs. BDD-PS systems

Applying a statistical design to the DSA-Cl_2 [7] and BDD-PS systems made it easier to identify the optimal operating parameters in each system. In the case of the DSA-Cl_2 system, it was noteworthy that the optimum values of the two operational variables were outside the experimental domain. This circumstance highlighted the need to select the central point as the best condition, especially intending to minimize specific energy consumption (SEC) and obtain removal rates of over 70% for both progestins. In contrast, for the BDD-PS system, the critical point, as estimated by the model, aligned with the experimental domain. Nevertheless, the conditions of the central point were employed in the treatment of real effluent from contraceptive production to allow a meaningful comparison between these two electro-oxidation systems. Table 3 compiles the findings.

The BDD-PS system showed removal efficiencies comparable to those of the DSA-Cl_2 system when applied to synthetic solutions; however, it was necessary to extend the electrolysis time in the BDD-PS system by 10 minutes to achieve concentrations below the detection limit for levonorgestrel (LNG) and gestodene (GES). This extension led to a 1.6-fold increase in electrical specific energy consumption (SEC) for the BDD-PS system, potentially suggesting the occurrence of competitive reactions among the hormones, reactive species, and other matrix components, i. e. dyes and surfactants (Table 3).

In a study conducted by Ding et al. [9], which examined the electrochemical activation of persulfate in BDD and DSA anodes for bisphenol A (BPA) degradation, it was observed that, in the case of real matrices, the efficiency of BPA degradation decreased, and the EEC increased in comparison to synthetic solutions. This phenomenon was attributed to the high concentrations of organic matter and the non-selective reactivity of the radicals.

Despite their comparable performance in terms of pollutant removal and consumption efficiency, the DSA-Cl_2 and BDD-PS systems behaved differently in the context of the eco-compatibility assessment (Table 3). Both systems showed high efficacy in reducing estrogenic activity, with the persulfate system standing out, which reached hormone concentrations below the detection limit of the YES test. On the other hand, both processes increased the acute toxicity to *D. similis* after treatment, with the BDD-PS system showing a more pronounced effect. As such, the eco-compatibility evaluation served as a valuable criterion to distinguish the superiority of the DSA-Cl_2 system over the BDD-PS system in the

Table 3
An overview of the degradation results for the progestins levonorgestrel (LNG) and gestodene (GES) in synthetic solutions and the residual effluent from contraceptive production. Conditions: $[LNG]_{0.RPW} = 1.02 \pm 0.05$ mg L^{-1} and $[GES]_{0.RPW} = 1.05 \pm 0.05$ mg L^{-1}.

References	[7]	Present study
Experimental variables	DSA-Cl_2 $[LNG]_0 = 1.05 \pm 0.03$ mg L^{-1} and $[GES]_0 = 1.10 \pm 0.17$ mg L^{-1} $j = 32.5$ mA cm^{-2} $[NaCl]_0 = 0.07$ mol L^{-1}	BDD-PS $[LNG]_0 = 0.97 \pm 0.14$ mg L^{-1} and $[GES]_0 = 1.06 \pm 0.30$ mg L^{-1} $[Na_2S_2O_8]_0 = 0.07$ mol L^{-1} $j = 37.5$ mA cm^{-2} $pH_0 = 6.75$
Synthetic solution - MIX		
Removal efficiency	LNG: 81.9 ± 7.1% GES: 74.9 ± 8.5%	LNG: 77.3 ± 8.7% GES: 87.5 ± 14.0%
SEC (kWh g^{-1})	2.2 ± 0.2 (6 min)	3.6 ± 0.8 (10 min)
k_{obs} (min^{-1})	LNG: 0.270 GES: 0.242	LNG: 0.133 GES: 0.299
Acute toxicity (*D. similis*)	$UT_{0'} = 2.5 \pm 0.4$ 100/EC50% $UT_{20'} = 12.6 \pm 1.5$ 100/EC50%	$UT_{0'} = 2.6 \pm 0.1$ 100/EC50% $UT_{30'} = 52.1 \pm 2.6$ 100/EC50%
Estrogenic removal (%) and residual value (E2-EQ ng L^{-1})	74.6% 234 ± 12	100% ≤ LD 5.9–2.34
Real Pharmaceutical Wastewater		
Removal efficiency	LNG: 83.1 ± 0.9% GES: 75.1 ± 2.8%	LNG: 58.6 ± 0.5% GES: 80.3 ± 0.7%
k_{obs} (min^{-1})	LNG: 0.235 GES: 0.204	LNG: 0.081 GES: 0.202
SEC (kWh g^{-1})	2.32 ± 0.03 (6 min)	2.4 ± 0.2 (10 min)
Cost	US$ 0.25 m^{-3}	US$ 0.31 m^{-3}

degradation of LNG and GES in mixture.

Olmez-Hanci et al. [27] investigated the toxicity of the most used oxidants AOPs and their sequestering agents, including persulfate and peroxymonosulfate. To this end, three classes of test organisms were used: *Vibrio fischeri, D. magna* and *Raphidocelis subcapitata*. The authors evaluated the effect of concentrations and exposure time, with persulfate (2.5–50 mmol L^{-1}) causing an 85% reduction in the mobility of *D. magna* during two hours of exposure, being considered the most toxic of the oxidizing agents evaluated.

Finally, the BDD-PS system had a specific energy consumption cost approximately 24% higher than that of the DSA-Cl_2 system. However, it is worth noting that the cost indicators of both systems are consistent with the values found in the literature. For example, Nashat et al. [25] reported an estimated cost of US$ 0.55 per cubic meter for treating sulfamethazine solutions using the BDD-PS system for 30 minutes. Ding et al. [9] estimated a cost of US$ 0.17 m^{-3} for treating BPA solutions with the same system over a 15-minute. In a separate study, Duarte et al. [11] estimated the cost of degrading the hormone methyl testosterone through anodic oxidation using a DSA electrode in conjunction with the supporting electrolytes $NaClO_4$ and Na_2SO_4, resulting in costs of US$ 10.81 m^{-3} and US$ 11.44 m^{-3}, respectively.

4. Conclusions

This research provides a valuable contribution to the field of electrochemical advanced oxidation wastewater treatment, especially about the removal of emerging contaminants as the widely used hormones levonorgestrel (LNG) and gestodene (GES). We evaluated a treatment approach involving the generation of sulfate and hydroxyl radicals in a singular reactor equipped with a boron-doped diamond (BDD) anode in continuous flow operation, using $Na_2S_2O_8$ (PS) as the support electrolyte.

A suitable and reliable mathematical model, based on the response surface methodology, highlighted the most promising conditions for operating the electrochemical process to achieve the lowest specific energy consumption (SEC), with the effects of the operating variables following the order current: density (j) > initial pH (pH_0) > initial sodium persulfate concentration ($[Na_2S_2O_8]_0$). Among them, the negative effect of pH contributed to the oxygen evolution reaction and the generation of sulfate radicals from acid catalysis. The BDD-PS system was improved at $[Na_2S_2O_8]_0 = 0.07$ mol L^{-1}, $j = 37.5$ mA cm^{-2} and $pH_0 = 6.75$, achieving high removal rates of progestins and low SEC during a 30-minute process, in synthetic and real pharmaceutical wastewater. For example, in the RPW, the BDD-PS system resulted in removals of 83.1 ± 0.9% of LNG and 75.1 ± 2.8% of GES, which promoted a SEC of 2.32 ± 0.02 kWh g^{-1}, corresponding to US$ 0.25 m^{-3}.

In addition, eco-compatibility tests were employed to verify the effect of by-product generation on acute toxic and estrogenic activity. The first case showed the substantial impact of the support electrolyte. On the other hand, the presence of persulfate in the solution provided 100% reduction of the initial estrogenic activity observed.

Finally, a comparison was also made with previous results we reported for the same system, with a different anode (DSA) and support electrolyte (NaCl). Due to the similarity of the anodic oxidation processes with regard to progestin removal efficiency, cost and lower SEC, acute toxicity and estrogenic activity removal were the tools that highlighted the use of active chlorine species as the best electrochemical process for the progestins degradation.

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CRediT authorship contribution statement

Allan dos Santos Argolo: Methodology, Formal analysis, Data curation. **Juliana Mendonça Silva de Jesus:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daniele Maia Bila:** Supervision, Resources. **Flávio Kiyoshi Tominaga:** Methodology, Data curation. **Sueli Ivone Borrely:** Supervision, Resources, Methodology. **Antonio Carlos Silva Costa Teixeira:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Juliana Mendonca Silva de Jesus reports financial support was provided by Coordination of Higher Education Personnel Improvement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The authors are unable or have chosen not to specify which data has been used.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jece.2024.113095.

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