ELECTROCHEMICAL AND SPECTROPHOTOMETRIC STUDY OF OLANZAPINE IN THE BUFFER SOLUTION AND THE EFFECT OF THE SOLVENT ON ITS COMPLEX FORMATION ABILITY

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Abstract: *The electrochemical and spectrophotometric behavior of Olanzapine (OLZ) was studied for its optimal concentration ratio towards citrate buffer solution, the half-wave potential of a mercury dropping electrode, and electrochemical and spectrophotometric calibration curves for the qualitative and quantitative determination of OLZ. The influence of various solvents on the ability of OLZ to form complexes with metals has been evaluated using the quantum-chemical semi-empirical AM1 method. The energetic, electronic, and structural characteristics of the molecule have been calculated, and the donor atoms in the OLZ molecule and the rules of its coordination with the metal atom have been identified. These studies are vital for further research evaluation of OLZ presence in blood plasma and urine. The removal of OLZ from model solutions was tested using the carbonaceous materials of hazelnut and walnut shells (obtained by our method), and their adsorption capacity was compared with industrial carbon material - Activated Birch Carbon (BAU-A) - showing compatible results.*
Keywords*: olanzapine, carbonaceous materials as adsorbents, voltammetrical study, spectrophotometrical study, complex formation, donor atom*
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Introduction

Olanzapine (OLZ) is a psychotropic drug derived from thienobenzodiazepine. It was first synthesized under the name Zyprexa. OLZ is used in the treatment of schizophrenia and mental disorders in adolescents and adults [1]. It is also currently used in the treatment of COVID-19 with psychotic polymorphic symptoms [2]. 40,469 patients were diagnosed with COVID-19, among whom 22.5% patients had neuropsychiatric manifestations. The most common neurologic manifestations included headache (3.7%) and sleep disorders (3.4%), Encephalopathy (2.3%), Stroke and transient ischemic attack (TIA) (1.0%) and 0.6% had seizures [3]. The incidence of any psychiatric diagnosis within 14–90 days of COVID-19 diagnosis was 18.1%, including 5.8% who were newly diagnosed [4]. OLZ has the ability to combine well with serotonin and dopamine receptors, activating them, which in turn promotes chemical balance in the brain. It should also be noted that even small doses of OLZ are characterized by high activity [1]. The scientific literature describes several methods for analysis of investigated drugs in pharmaceutical formulations (including biological fluids and flow injection titration, voltammetry, gas chromatography, high performance liquid chromatography, capillary zone electrophoresis, HPTLC, X-ray powder diffraction, and Spectrophotometry), that require expensive devices and reagents [5-10].

Therefore, *the aim of* the present work was, first, to design an economical and simple method with relatively inexpensive and readily available reagents and, second, to investigate cheap and available adsorbents and economical routes for the subtraction of OLZ. This work establishes the possibility of using instrumental methods for the quantitative determination of OLZ. We studied the processes of cathodic reduction of this preparation on a mercury drop electrode.

A spectrophotometric method for the determination of OLZ described in the literature is based on the diazo coupling of OLZ with diazotized *p*-nitroaniline in an alkaline medium, forming a stable water-soluble brown azo dye with a maximum absorption at 405 nm. Beer-Bouguer-Lambert's law is obeyed over the concentration range of (0.5 ÷ 45.0 μg/mL) and Sandell's sensitivity value was 0.0198 μg/cm^2 [11]. The work of spectrophotometric determination of OLZ based on the formation of a yellow condensation product with p-dimethylaminobenzaldehyde, followed by measurement of absorption at 410 nm, is also known. The calibration graph was linear between 5 and 160 g/mL, and the calculated Sandell sensitivity was 49.50 ng/cm^2. The limits of detection and quantification were 6.6 and 20 μg/mL, respectively [12]. The methods of analysis of OLZ are based on the oxidation of OLP by a measured excess of cerium (IV) sulphate in H_2SO_4 medium. This was followed by determination of the unreacted oxidant by reacting with either N-phenylanthranalic acid (NPA) and measuring the absorbance at 440 nm (Method A) or sulphanilic acid (SAA) and measuring absorbance at 545 nm (Method B). In both methods, the amount of cerium (IV) sulphate reacted corresponds to the amount of OLZ. The calibration graphs were linear over the ranges 0.3 ÷ 1.8 and 5.0 ÷ 75.0 μg/mL OLP for method A and method B, respectively [13].

From the point of view of complex formation, the OLZ molecule is interesting as an organic ligand containing donor atoms, and in addition, the synthesis of complex compounds with some "metals of life" based on it is undoubtedly novel. It is also important to study the physicochemical properties of the synthesized compounds and compare their physiological activity with the free ligand.

The European Commission (2000/60/EC) recognized pharmaceuticals as new persistent organic pollutants (PoPs), which are not routinely detected in water quality testing [14-16]. It is necessary to process pharmaceutical waste, which will lead to a decrease in its quantity in water systems and soil [17]. Despite the low concentrations of pharmaceuticals in water and soil, they lead to serious negative consequences for the health of animals and humans (endocrine, hormonal, and genetic disorders, etc.), causing worldwide concern [18]. Modern scientific interest is directed towards the deactivation of multifunctional pharmaceutical compounds; therefore, research is being conducted aimed at increasing the efficiency of existing purification mechanisms and at developing completely new methods [19-22].

The use of adsorbents based on agro-waste for the removal of pharmaceuticals from wastewater is becoming increasingly relevant and extremely important.

Experimental part

Voltammetric studies. Our previous voltammetric studies showed that OLZ does not exhibit electrochemical activity in 0.5 mol/L aqueous and ethanol solutions of NaClO4, so we continued to study its electrochemical properties in a buffer solution. The studies were conducted on a Model 1100C potentiostat/galvanostat (USA). A mercury dropping electrode was used as the working electrode, a saturated calomel electrode was the reference electrode, and a platinum electrode was the anode. The supporting electrolyte was a buffer solution consisting of 0.08 mol L^{-1} citric acid ($C_6H_8O_7$) and 0.05 mol L^{-1} trisodium citrate ($Na_3C_6H_5O_7$)**;** the dropping time was seven drops per minute, the mass of one drop was 0.00133 g**,** the height of the mercury column was 59 cm**,** the capillary diameter was 8.56 μm**,** and the average velocity of mercury in the capillary was 0.20 m s^{-1}**.**

Spectrophotometric studies. A simple and economical spectrophotometric method was developed for the determination of olanzapine. The ZUZI spectrophotometer model 4201/50, whose wavelength is digitally adjustable in the range of 200-1000 nm, was used to conduct the experiment. The spectrophotometer reads absorbance, conductance, and concentration (standard curve method) and is equipped with the 10 mm quartz cuvettes we use.

A solution containing 0.08 mol/L citric acid and 0.05 mol/L trisodium citrate (background solution) was selected as a comparable solution and as a solvent for OLZ. For a solution with the maximum concentration of olanzapine (6.4 10^{-4} mol/L) in a background solution (0.08 mol/L citric acid and 0.05 mol/L trisodium citrate), taken curves of dependence of the optical absorbance on wavelength in the range 340 – 650 nm with a 30 nm band. To improve the accuracy of the experiment, the step was reduced to 2 nm in the region of the maximum optical absorption value. The maximum absorbance value was detected at 362 nm (Fig. 4).

Sorption studies. At the Ivane Javakhishvili TSU R. Agladze Institute of Inorganic Chemistry and Electrochemistry, a technological method to obtain cheap, high-quality, eco-friendly carbon material with defined and unique properties from plastics and household waste containing cellulose fibers (wood sawdust, hazelnut and walnut shells, etc.) was developed. On which a patent has been issued by the National Center for Intellectual Property of Georgia [23]. The obtained carbon sorbents were tested for the extraction of heavy metal ions and organic and biological pollutants from water [24-27]. Adsorption investigations were carried out to obtain the optimal conditions with multiple swings of process variables. The experiments were performed employing contact time (1–10 min), adsorbent particle size (40 μm), adsorbent dose (0.5–1.0 g), solution concentration ($2.56 \cdot 10^{-4}$ mol/L). The observation was carried out under static conditions at a constant temperature of 25ºC. The solution was separated from the sorbent by filtration. After filtration, the amount of olanzapine was determined by spectrophotometer Zuzi 4201/50 in 362 nm. The amount of adsorbed paracetamol was calculated according to the mass balance [28], and the rate of extraction (S, %) of paracetamol by the sorbent was calculated by the formula below [28]:

$$q = \frac{(C_0 - C_e)V}{W} \quad (1); \qquad S = \frac{(C_0 - C_e)}{C_0} x100\% \quad (2)$$

Where, q is the adsorption value, mg/g; V is the volume of solution, L; C_0 and C_e are initial and equilibrium concentrations, mg/L; W is the mass of adsorbent, g; and, S is rate of extraction, %.

Results and discussion

Using cyclic voltammetry, we obtained voltammetric curves of OLZ in the potential range E = 0.0 – -2.5 V, which are shown in Fig. 1.

Using the Geyrovsky-Ilkovich method [29], the dependence lg (I / (I_d –I)) on the electrode potential (E) (Fig. 2, A) was constructed, where I_d and I - represent the corresponding currents of the limiting and selected potentials (E). It has been established that the half-wave potential of the half-wave of OLZ in the system under study is $E_{1/2}$ = -1.51 V. Using the slope (tgα = n/0.059) obtained from the linear dependence of lg (I / (I_d – I)) on the potential (E), the number of electrons involved in the electrochemical reaction was calculated (n = 0.34). The height of the diffusion wave is directly proportional to the concentration of OLZ, which makes it possible to determine it within concentrations of $3.2 \cdot 10^{-5} \div 2.56 \cdot 10^{-4}$ mol/L (Fig.2, B). Figure 3A shows the dependence of the optical absorbance on wavelength. The method is based on obtaining a yellow-colored condensation product with citric acid and trisodium citrate and then measuring the absorbance density at 362 nm.

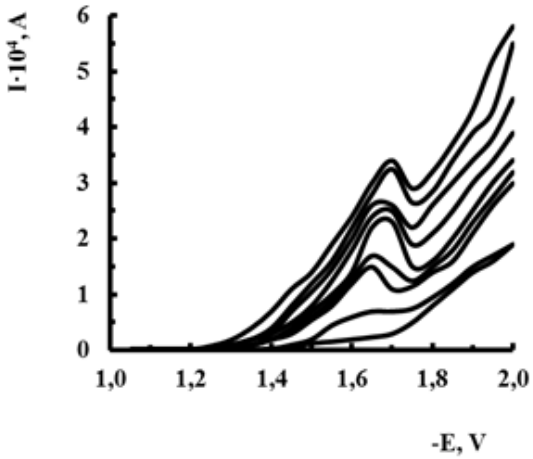
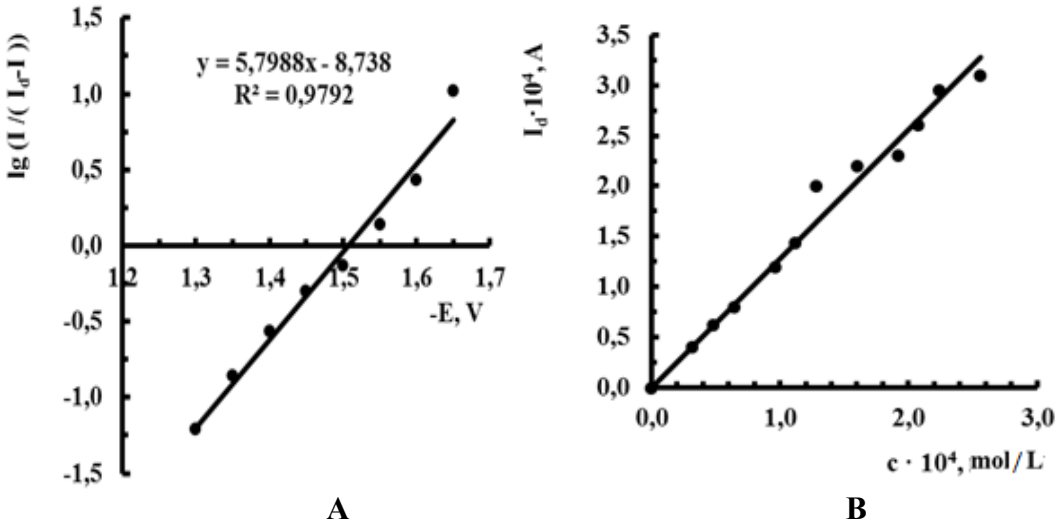


Fig. 1. Voltammetric curves of a buffer solution [a mixture of 0.08 mol/L citric acid ($C_6H_8O_7$) and 0.05 mol/L trisodium citrate ($Na_3C_6H_5O_7$)] with various additives of OLZ: 1 - 0; 2 - 3.2 · 10^{-5}; 3 - 6.4 · 10^{-5}; 4 - 9.6 · 10^{-5}; 5 - 1.28 · 10^{-4}; 6 - 1.6 · 10^{-4}; 7 - 1.92 · 10^{-4}; 8 - 2.24 · 10^{-4}; 9 - 2.56 · 10^{-4} mol/L.



A **B**

Fig. 2. (A) Determination of the half-wave potential E1/2 of OLZ in a buffer solution; (B) Calibration curve for OLZ (E = -1.7 V)

At the wavelength of 362 nm, the optical absorption of concentrations below the maximum is investigated. For each concentration, the optical absorption data were taken 3 times, and the average value of optical absorption was calculated. Repeatability was 99-100%.

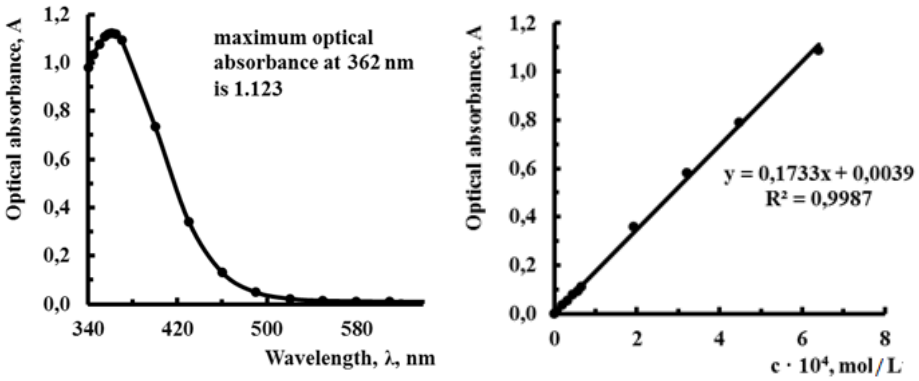
To study the optical absorption, solutions were prepared in the concentration range of $6.4 \cdot 10^{-8} \div 6.4 \cdot 10^{-4}$ mol/L. In the concentration ranges of $6.4 \cdot 10^{-6} \div 6.410^{-4}$ mol/L, the absorption spectrum curve allows it to be used as a calibration curve because the optical absorption values increase linearly with the increase in OLZ concentration (Fig. 3 (B)). The degree of reproducibility is 98-103%, and the degree of precision varies within 3%.

Molar absorption (extinction coefficient) was calculated, as in [30], using the formula:

$$A = \varepsilon \cdot c \cdot l, \quad \varepsilon = A / (c \cdot l)$$

where *A* is optical absorption; ε is molar absorption (extinction coefficient (1/(mol·cm)), c is concentration (mol/L), and l is distance that the beam travels in solution (cm).

$\varepsilon = (A_{max} - A_{min}) / [(c_{max} - c_{min}) \cdot l]$;
$\varepsilon = (0.1126 - 0.0108) / [(6.4 \cdot 10^{-4} - 6.4 \cdot 10^{-6}) 1] = 16\,0.67$ 1/(mol·cm)



A **B**

Fig. 3. (A) Optical absorption spectrum curve of 6.4 10^{-4} mol/L OLZ in 0.08 mol/L citric acid and 0.05 mol/L trisodium citrate; (B) Calibration curve for OLZ (λ = 362 nm).

Table 1. Quantitative parameters of OLZ obtained by the spectrophotometric method

Parameter	Meaning
Operating wavelength, nm	362
Concentration corresponding to the straightness range, mol/L	$6.4 \cdot 10^{-6} \div 6.4 \cdot 10^{-4}$
Molar absorption (extinction coefficient), (1/mol* cm)	160.67
Lower detection limit, mol/L	$6.4 \cdot 10^{-8}$
Upper limit of quantification of OLZ, mol/L	$6.4 \cdot 10^{-4}$

The OLZ molecule has been studied by the quantum-chemical semi-empirical AM1 method both in the gaseous state and in various solvents - water, ethanol, acetone, dimethyl sulfoxide, chloroform, and hexane. The heat of formation of the molecule (Fig. 4), the value of the total energy, ionization potential, dipole moment, interatomic distances, valence angles, bond lengths, effective charges on atoms, electron density on atoms, and electron occupancy in atomic orbitals have been calculated.

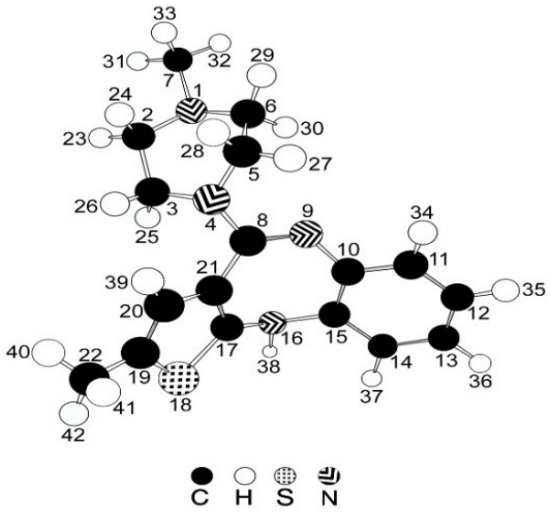


Fig. 4. Numbering of atoms in the olanzapine molecule

The values obtained as a result of calculations in solvents are compared with similar values obtained in the gas phase, and as a result of certain conclusions, the most favorable mechanism for complexation of the OLZ molecule (ligand) with metals and the optimal conditions for conducting the synthesis are suggested [31-34].

According to quantum-chemical calculations, the heat of formation of the OLZ molecule is lower in solvents than in the gaseous state, meaning that the solvent contributes to the stability of the complex (Table 2). (Water, μ=3.938; DMSO, μ=4.374; Methanol, μ=3.814; Ethanol, μ=4.135; Acetone, μ=3.704; Chloroform, μ=3.236; Hexane, μ=3.075; Citric acid, μ= 4.178). The larger the value of the dipole moment, the more stable the molecule (dimethylsulfoxide - μ=4.374) [31-33]. Analysis of the effective charges of the nitrogen N(16) atom and the electron densities on the atoms, as well as the distribution of electrons on the orbitals, showed that only in three solvents (water, methanol, acetone and citric acid) the nitrogen N(16) atom can exhibit donor properties: an electron pair is located on the 2s orbital, and the second pair of electrons is located on the $2P_x$ orbital, which allows this atom to form a chemical bond with the metal-complexing agent. In the remaining solvents - DMSO, ethanol, chloroform, and hexane - the electron pair of the nitrogen N(16) atom is located not on the $2P_x$, but on the $2P_y$ and $2P_z$ orbitals, which makes it impossible for this atom to participate in the complex formation process [36]. According to the analysis of quantum-chemical calculations, the sulfur atom S(18) should have shown the ability to form bonds with metal atoms, but the positive charge of the S(18) atom excludes the possibility of this atom forming chemical bonds with metal atoms. To clarify the values of the thermodynamic stability of the molecule, the distribution of electrons on orbitals, and the lengths of interatomic bonds (distortions/errors were observed), the results obtained by the quantum-chemical semi-empirical AM1 method were additionally verified by the MP3 and MNDO-d methods.

The removal rate of olanzapine (OLZ) (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine) had been assessed using these abovementioned sorbents. The studies had shown that the best adsorption is achieved at a solution with a concentration of $2.56 \cdot 10^{-4}$ mol/L after 3 minutes. The maximum amount of olanzapine that can be bound by 0.5 g of sorbent in a 50 ml solution is 98.55% (in the first 3 minutes). An increase in the amount of adsorbent is reciprocated in the value of sorption efficiency (100%) by largely improving it.

Table 2. Heat of formation (ΔH), dipole moments (μ) values in the OLZ molecule

Solvent	Heat of formation, kJ/mol	Dipole moment, Debye
Gas	440.425	2.098
H_2O, water	384.282	3.938
C_2H_6SO, dimethyl sulfoxide (DMSO)	375.310	4.374
CH_3OH, methanol	382.383	3.814
C_2H_5OH, ethanol	378.576	4.135
$(CH_3)_2CO$, acetone	385.283	3.704
$CHCl_3$, chloroform	401.987	3.236
C_6H_{12}, hexane	424.601	3.075
$C_6H_8O_7$, citric acid	378.556	4.178

Sorption capacity for BAU-A in comparison to hazelnut and walnut shells′ carbonaceous materials was comparable, however it was lower. Taking into consideration the high adsorption activity of carbonaceous materials prepared by us and the low cost (which is achieved by a one-stage process that does not require preliminary processing of raw

materials), these sorbents can be seen as a promising material for further studies.

In Table 3, presented below, the solvents are: 1-gas, 2-water, 3-DMSO, 4-methanol, 5-ethanol, 6-acetone, 7-chloroform, 8-hexane, and 9-citric acid.

Table 3. Values of dielectric permittivity (ε), atomic charges (q), electronic charges, and atomic orbital electron distribution (s,p) in the OLZ molecule

Atom	Solvent	Charge on the atom	Electron density on atom	n	Distribution of electrons across orbitals			
					nS	nP_x	nP_y	nP_z
N(1)	1	-0.261	5.261	2	1.587	1.057	1.139	1.478
	2	-0.279	5.279	2	1.595	1.071	1.147	1.466
	3	-0.298	5.298	2	1.598	1.078	1.132	1.489
	4	-0.281	5.281	2	1.597	1.073	1.126	1.485
	5	-0.296	5.296	2	1.594	1.077	1.132	1.491
	6	-0.278	5.278	2	1.598	1.073	1.135	1.471
	7	-0.279	5.279	2	1.592	1.070	1.115	1.502
	8	-0.273	5.273	2	1.593	1.069	1.080	1.530
	9	-0.293	5.293	2	1.598	1.077	1.126	1.492
N(4)	1	-0.220	5.220	2	1.568	1.353	1.047	1.253
	2	-0.237	5.237	2	1.604	1.262	1.194	1.177
	3	-0.239	5.239	2	1.604	1.338	1.043	1.255
	4	-0.230	5.230	2	1.609	1.264	1.176	1.180
	5	-0.236	5.236	2	1.605	1.326	1.058	1.247
	6	-0.230	5.230	2	1.608	1.265	1.176	1.181
	7	-0.225	5.225	2	1.607	1.282	1.126	1.210
	8	-0.229	5.229	2	1.602	1.343	0.984	1.301
	9	-0.235	4.235	2	1.608	1.306	1.095	1.225
N(9)	1	-0.230	5.230	2	1.684	1.147	1.115	1.284
	2	-0.232	5.232	2	1.685	1.124	1.366	1.057
	3	-0.249	5.249	2	1.681	1.143	1.286	1.140
	4	-0.231	5.231	2	1.683	1.127	1.366	1.055
	5	-0.245	5.245	2	1.682	1.140	1.301	1.122
	6	-0.230	5.230	2	1.683	1.124	1.364	1.060
	7	-0.222	5.222	2	1.682	1.126	1.347	1.066
	8	-0.214	5.214	2	1.682	1.181	1.174	1.178
	9	-0.240	5.240	2	1.683	1.130	1.325	1.102
N(16)	1	-0.184	5.184	2	1.525	1.068	1.517	1.073
	2	-0.216	5.216	2	1.549	1.383	1.263	1.021
	3	-0.221	5.221	2	1.546	1.280	1.323	1.074
	4	-0.220	5.220	2	1.546	1.359	1.307	1.008
	5	-0.221	5.221	2	1.543	1.291	1.331	1.056
	6	-0.220	5.220	2	1.543	1.372	1.292	1.013
	7	-0.209	5.209	2	1.540	1.324	1.331	1.013
	8	-0.199	5.199	2	1.530	1.150	1.372	1.147
	9	-0.217	5.217	2	1.549	1.308	1.319	1.040
S(18)	1	0.482	5.518	3	1.819	0.940	1.446	1.313
	2	0.663	5.337	3	1.816	1.594	1.018	0.910
	3	0.652	5.348	3	1.818	1.572	1.065	0.894
	4	0.642	5.358	3	1.818	1.604	1.026	0.911
	5	0.633	5.367	3	1.818	1.585	1.066	0.898
	6	0.629	5.371	3	1.818	1.611	1.030	0.912

	7	0.569	5.431	3	1.818	1.630	1.063	0.920
	8	0.514	5.486	3	1.819	1.527	1.189	0.951
	9	0.646	5.354	3	1.818	1.589	1.049	0.899

Conclusion

1. The voltammetric activity of OLZ in a buffer solution (a mixture of 0.08 M citric acid and 0.05 M trisodium citrate) was revealed at cathodic polarizations of a mercury drop electrode, in contrast to neutral aqueous and ethanol solutions of sodium perchlorate;
2. The half-wave potential of OLZ in a buffer solution was calculated, and is equal to $E_{1/2}$ = -1.51 V;
3. The range of concentrations ($6.4 \cdot 10^{-6} \div 6.4 \cdot 10^{-4}$ mol/L (2÷20 mg/L) was established for the quantitative determination of OLZ from the constructed calibration curve;
4. By measuring the optical density at a wavelength of 362 nm, the regression dependence of the photometric optical density on the concentration of OLZ was determined, and a calibration curve was constructed;
5. The ability of the olanzapine molecule to form complexes with metals has been studied using the semi-empirical AM1 quantum-chemical method; the energetic, electronic, and structural characteristics of the molecule in the gas phase as well as in water and various organic solvents have been calculated;
6. Donor atoms have been identified. According to quantum-chemical calculations, nitrogen atoms N(4), N(9), and N(16) have the ability to form a chemical bond with a metal complexing agent;
7. Based on the analysis of the results of quantum-chemical calculations, a solvent has been pre-selected for the synthesis under optimal conditions; in particular, in the case of synthesis in water, methanol, and acetone, the nitrogen atom N(16) in the OLZ molecule will exhibit donor properties and will participate in the formation of a chemical bond;
8. The results of the studies showed that the obtained adsorbents (carbonaceous materials of hazelnut and walnut shells) can be used for efficient removal of olanzapine from aqueous systems.

Such research is of great importance for planning the synthesis of complex compounds based on OLZ, for selecting the solvent, and for studying various properties. The findings showed that activated carbonaceous materials obtained are effective and cheap, compatible adsorbents to be used to overcome the pharmaceutical pollution in wastewater.

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Conflict of interest

The authors announced that there are no conflicts of interest regarding this current work.

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