

# Development of a Method for Multisensory Stripping Voltammetry in the Analysis of Medical Preparations

Irina Kolesnichenko\*

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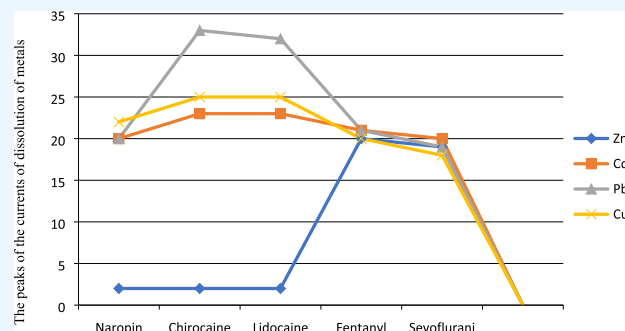
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**ABSTRACT:** For the effective dosage of newly developed ophthalmic drugs, an assessment of the dynamics of their concentration in lacrimal fluid over time is required. To express the detection and identification of drugs, new methods are needed that must meet numerous requirements, not the least of which are selectivity, speed, the absence of false-negative results, and cost-effectiveness. The possibility of identifying anesthetics (sevoflurane) in lacrimal fluid has been studied using a new electrochemical method of multisensory inversion voltammetry in the electronic tongue and electronic nose format. The measurements were performed on a planar electrode, which is a three-electrode structure. The solution of the test system consisted of 0.05 M KCl, which contained the metal cations  $Zn^{2+}$ ,  $Cd^{2+}$ ,  $Pb^{2+}$ ,  $Co^{2+}$ , and  $Hg^{2+}$  at a concentration of  $5 \times 10^{-5}$  M. It is shown that this method is effective for the determination of anesthetics, and the dynamics of changes in their concentration over time are examined. This study aimed to research the behavioral pharmacokinetics in the lacrimal fluid of the opioid drug sevoflurane in pediatric ophthalmology using multisensory stripping voltammetry in patients during strabismus correction surgery. The dynamics of changes in their concentrations over time were examined. After the instillation of the anesthetics in patients, their concentrations in the tear fluid remained unchanged within 10 min. The list of organic substances that can be determined by multisensory stripping voltammetry has been extended. The class of organic substances determined by the method of multisensory inversion voltammetry has been expanded.



## 1. INTRODUCTION

Nowadays, drip chemical analysis, thin-layer chromatography, and mass spectroscopy are mainly used for the identification and comparative analysis of drugs. These methods have some disadvantages, the most significant of which are multistage, a high percentage of false-positive reactions, bulkiness of equipment, a small degree of mobility, a significantly sized test sample, the complexity of the sample preparation stage, and the requirement of a highly qualified performer.

This work aimed to study, using multisensory stripping voltammetry, the pharmacokinetic behavior of some alkaloid-based drugs (sevoflurane) in the lacrimal fluid of ophthalmic patients undergoing strabismus correction surgery. Monitoring the drug concentration is vital for choosing the right dose. Such monitoring systems are based on the use of a given matrix sensor with completely different characteristics. The Institute of Physical Chemistry and Electrochemistry, named after A.N. Frumkin of the Russian Academy of Sciences, developed a method for multisensory stripping voltammetry. This method is based on the recognition of multidimensional images generated by the multisensory electrochemical systems that provide reliable information about the tested objects using multidimensional statistics. The measurements were performed by using a

flat solid-state electrode. The effectiveness of this method of determination is demonstrated by considering changes in the concentration over time. A multisensory stripping voltammetry procedure was developed and tested to determine the liquid concentration. The study also included the elaboration of an electrochemical multisensory test system that provides the express analysis of alkaloids (exemplified by sevoflurane) in electronic tongue format by stripping voltammetry on a single electrode.

## 2. MATERIALS AND METHODS

**2.1. Modern Methods for Alkaloid Analysis.** Because of the specific features of narcotic drugs and psychotropic substances, special methodological approaches are necessary to solve this task. The following methods of analysis are mainly

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used: gas chromatography, mass spectrometry, drip chemical analysis, and electrochemical methods.

Mass spectrometry is a method of analyzing a substance by determining the ratio of the mass of charged particles to their charge ( $m/z$ ) and the relative number of ions obtained during ionization of the substance under study or already present in the mixture under study.<sup>1,2</sup> The disadvantage of the mass spectrometric method is the need for a preliminary independent approximate assessment of the determined concentration for dosing the optimal amount of the isotope standard. Mass spectrometry is one of the most expensive methods of analysis. This is mainly because of the need to organize high vacuum inside the device and the associated difficulties in choosing equipment.

**2.2. Molecular Absorption Methods for Determination.** Several studies<sup>3–5</sup> have described the use of 2-benzoylpyridine thiosemicarbazone, 5-(2-benzothiazolazo)-8-hydroxyquinoline, 2,6-diacetylpyridine-bis-4-phenyl-3-thiosemicarbazone, 1-ethyl-6-fluoro-4-oxo-7-piperazine-1-yl-1*H*-quinoline-3-carboxylic acid, 4-hydroxy-3,5-dimethoxybenzaldehyde-4-hydroxybenzoyl hydrazone, and so on for the spectrophotometric determination of zinc. Generally, the range of detectable concentrations is 0.02–4  $\mu\text{g/mL}$ , and the detection limit is 0.0081–0.064  $\mu\text{g/mL}$ .<sup>6,7</sup> Regarding the spectrophotometric determination of zinc, cobalt, and so on, one review was devoted to plants, milk, alloys, pharmaceuticals, soil, water, vegetables, vitamin B12, and food products.<sup>8–10</sup>

A research<sup>11</sup> presents a technique for the fluorimetric analysis of thiocyanate ions using 2,7-dichlorofluorescein in blood serum and saliva. The determinations were carried out at  $\lambda = 524$  nm and  $\text{pH} = 5.8$ – $6.7$ ; the linearity range was from 1.0 to 60 ng/mL and the detection limit was  $-1.0$  ng/mL. Fluorescent techniques allow the determination of sulfide and sulfite ions at 10–7 mol/L, tungstate ions at 0.14 ng/mL, and hydrophosphate ions at 2.26–102 mg/L.<sup>12–15</sup> The main disadvantages of spectrophotometric methods are that they require specific reagents, volatile solvents, and long-term sample preparation, do not always have good selectivity, and have a narrow range of detectable concentrations. Highly qualified employees are required.

**2.3. Optical Methods of Determination.** One of the most common methods for determining sulfate ions in precipitation, river waters, lakes, and soil is turbidimetry, which often does not allow reproducible results.<sup>16,17</sup> X-ray fluorescence analysis is widely used for the determination of metals,<sup>18,19</sup> which allows the recognition of any element, has wide linear ranges of concentrations, is expressive, and does not require the destruction of the analyzed compound or the separation of elements. Simultaneously, the analysis has a low permeability of X-rays through the thickness of the sample, has mutual influence on the components of the analyzed substance, and requires expensive equipment.

Atomic absorption and atomic emission spectroscopy refer to atomic absorption, and atomic emission spectroscopy is among the most widely used methods for determining the metal content in various objects (food products, alloys, and waters<sup>20,21</sup>). Among the optical methods for the determination of selenium in vegetables, fruits, and dairy products,<sup>22</sup> molybdenum(VI), tungsten(VI) in ores, biological objects in steels and alloys,<sup>23</sup> Atomic absorption spectroscopy (AAS) and NPP are widely used, often with preliminary separation, concentration, or extraction<sup>24–26</sup> of the analyzed elements. Despite this, AAS and NPP have some significant disadvantages, including high equipment and operating costs (for NPP: high-

purity argon), the need for special training of personnel, and the need for a separately equipped room.

**2.4. Chromatographic Determination of the Inorganic Anions.** Ion chromatography (IM) is widely used in the ecological analysis of waters, to which several reviews have been devoted.<sup>27,28</sup> These reviews provide information about the methodological aspects of the separation and determination of both single-charge and double-charge anions (sulfate, sulfite, selenite, molybdate, and tungstate ions). This study is devoted to the determination of carbonate ions in tap water and bath salts by using this method. However, combined methods of determination have become the most widespread when chromatography is used to separate only a mixture of ions. For further determination, mass spectrometry, visible or UV spectrometry, AAS, NPP, amperometry, or conductometry were used.<sup>29,30</sup>

A method for the rapid and sensitive determination of selenite ions in human urine is proposed. Tetraethyl borate and sodium tetraphenylborate were used as reagents for isolating selenite from human urine. The developed technique makes it possible to determine selenite ions at the level of 0.05 g/L of urine.<sup>31</sup> The method of high-performance liquid chromatography with mass spectrometry can be used to determine the molybdate, tungstate, and phosphate ions in groundwater and soil extracts, as described in.<sup>32</sup> However, it is applicable for the analysis of gaseous, liquid, and solid substances with a molecular weight less than 400, which must meet certain requirements, the main of which are volatility, thermal stability, and inertia. These requirements are fully met, as a rule, by organic substances; therefore, gas chromatography is widely used as a serial method for the analysis of organic compounds.

Despite the widespread use of chromatography, its following disadvantages can be distinguished: the need for expensive equipment and consumables. The combination of chromatography with optical, electrochemical, and mass spectral methods helps individual selection of the detection method, while common detection methods do not always allow observers to determine trace amounts of anions.

Capillary electrophoresis is used to separate complex mixtures consisting of ions or molecules. The process is characterized by expressiveness, high separation efficiency, low consumption of reagents and materials, simple sample preparation, and low cost of analysis and equipment.<sup>33</sup> The method of capillary electrophoresis<sup>34</sup> with UV detection (at  $\lambda = 229$  nm) was used to determine sulfides in wastewater from the leather industry. The detection limit was 10  $\mu\text{g/L}$ . Capillary electrophoresis has also found application in the analysis of food products.<sup>35</sup> Initially, sulfite ions are oxidized to sulfates, which are determined by the UV spectrometric method at  $\lambda = 254$  nm. The limit of detection of sulfites in food was 5 mg/kg.

The review<sup>30</sup> is devoted to the application of capillary electrophoresis by  $\text{sUF}^-$ , conductometric, and mass spectrometric detection for separating sulfur-containing anions. The following order of anion migration was determined:  $\text{S}_2\text{O}^{32-} \leq \text{SO}^{42-} \leq \text{S}^{2-} \leq \text{SO}^{32-}$ , which was determined in beverages, vinegar, technological solutions for the production of kraft paper and extracts from clay soils. The main disadvantages of electrophoresis include inapplicability for the analysis of samples that practically do not dissolve in aqueous or water–alcohol solutions, has relatively low concentration sensitivity due to the short length of the optical path, and has retention time depending on the state of the inner surface of the capillary,

which reduces the separation efficiency and does not allow for achieving high definition accuracy.

The main disadvantages of electrophoresis include its inapplicability to the analysis of samples that practically do not dissolve in aqueous or water–alcohol solutions.

### 2.5. Electrochemical Methods for Determination.

Inversion voltammetry (IV) has high sensitivity, accuracy, and low detection limits and is considered a faster and more reliable method for determining the metal content in objects than AAS or NPP. Various variants of voltammetry are widely used to determine zinc and cobalt concentrations in nature: wastewater, food, medicines, biological objects, nanomaterials, and soil.<sup>36–39</sup>

Anode IV was used for the determination of zinc and cobalt–adsorption cathode IV. In,<sup>40</sup> the amount of zinc in tap water and food additives was determined using a graphite electrode. Analytical characteristics of the technique were as follows: linear concentration range  $-1 \times 10^{-6}$  to  $1 \times 10^{-4}$  mol/L, detection limit  $-5 \times 10^{-7}$  mol/L, and accumulation time  $-5$  min. Chromium(III), lead, and cadmium ions do not interfere with the determination of zinc, whereas copper, cobalt, and nickel ions strongly interfere. It was found<sup>41</sup> that the determination of cobalt is not hindered by a 25-fold excess of cadmium and a 10-fold excess of chromium(III), magnesium, aluminum, and iron(III). The detection limit of cobalt in the presence of eriochrome black T is  $5 \times 10^{-7}$  mol/L. Cobalt was determined in vitamin B12 and other alloys. Moreover, voltammetry is widely used to determine selenium(IV) and (VI);<sup>42,43</sup> to achieve this, we proposed the use of differential pulsed cathode voltammetry with a mercury-drop electrode with preliminary concentration and separation of selenium(IV) and selenium(VI). The detection limit was 10 ng/L for these elements. The authors<sup>44</sup> proposed a sensor based on a silver electrode. The linear range of detectable concentrations was 10–1000  $\mu$ mol/L of sulfide ions. The method has a detection limit of more than 10  $\mu$ mol/L and is used for monitoring hydrothermal vents. A new electrochemical Hg<sup>2+</sup>-sensing platform,<sup>45</sup> based on porous activated carbon (BC/Cu<sub>2</sub>O) modified with cuprous oxide, was developed using a simple impregnation pyrolysis method. Differential pulse anodic stripping voltammetry (DPASV) was used to investigate the sensing capability of the BC/Cu<sub>2</sub>O electrode toward Hg<sup>2+</sup>. Due to the excellent conductivity and large specific surface area of BC and the excellent catalytic activity of Cu<sub>2</sub>O nanoparticles, the prepared BC/Cu<sub>2</sub>O electrode exhibited excellent electrochemical activity. The high sensitivity of the proposed system resulted in a low detection limit of 0.3 ng L@1 and a wide linear response in the ranges from 1.0 ng L@1 to 1.0 mg L@1. In addition, this sensor was found to have good accuracy, acceptable precision, and reproducibility. These results show that the BC/Cu<sub>2</sub>O composite is a promising material for Hg<sup>2+</sup> electrochemical detection. In work,<sup>46</sup> the concentrations of Cd(II), Cu(II), and Fe(III) were determined in 13 brands of craft beer with the highest consumption in Quito, Ecuador, by DPASV using a boron-doped diamond (BDD) working electrode. The BDD electrode used had favorable morphological and electrochemical properties for the detection of metals, such as Cd(II), Cu(II), and Fe(III). The double-layer capacitance of the BDD electrode was 0.01412 F cm<sup>2</sup>, which was a relatively low value;  $I_{\text{pox}}/I_{\text{pred}}$  ratio was 0.99 for the potassium ferro-ferricyanide system in BDD, demonstrating that the redox process is quasi-reversible. The figures of merit for Cd(II), Cu(II), and Fe(III) were DL of 6.31, 1.76, and 1.72  $\mu$ g L@1, QL of 21.04, 5.87, and 5.72  $\mu$ g L@1, repeatability of 1.06, 2.43, and 1.34%, reproducibility of 1.61, 2.94, and 1.83% and

percentage of recovery of 98.18, 91.68, and 91.68%, respectively. It is concluded that the DPASV method for BDD has acceptable precision and accuracy for the quantification of Cd(II), Cu(II), and Fe(III). In work,<sup>47</sup> 3-(4-Nitrophenyl)-8-(2,3-dimethylphenyl)-7,8-dihydroimidazo[2,1-c][1,2,4]triazin-4(6H)-one (NDIT) is one of the most promising anticancer agents. Therefore, a sensitive and selective sodium dodecyl sulfate-modified screen-printed carbon sensor (SPCE/SDS) was used for its quantitative analysis. The sensor was characterized by CV and electrochemical impedance spectroscopy (EIS). Under the optimized conditions ( $t$  45 s, DE 175 mV, 150 mV/s, and 5 ms), the DPAdSV procedure with SPCE/SDS presented a very wide linear range from 1 to 2000 nM and a low detection limit of 0.29 nM. A 1000-fold excess concentration of potential interferents commonly present in biological samples did not significantly alter the peak current of NDIT. The practical application of the proposed DPAdSV procedure with SPCE/SDS was successfully verified by analyzing spiked human serum samples.

The protective effect of antioxidants<sup>48</sup> using electrochemical techniques can be evaluated by examining the oxidative changes in deoxyribonucleic acid (DNA) nucleobases. In this study, a gold nanoparticle (AuNP)-decorated and multiwalled carbon nanotube (MWCNT)-Nafion-modified glassy carbon electrode (GCE/AuNP/MWCNT-Nafion) was developed to evaluate the preventive ability of antioxidants against DNA damage. A modified working electrode was prepared and characterized by using cyclic voltammetry (CV), EIS, and scanning electron microscopy (SEM). Quercetin was found to show the highest antioxidant effect, and its limit of detection was determined as 1  $\mu$ M. In work,<sup>49</sup> a screen-printed, polymeric  $\beta$ -cyclodextrin ( $\beta$ -CD)-modified electrode, affording nanocavities for inclusion of the analyses, was shown as a disposable sensor capable of identifying bacteria by their metabolites. Three bacterial species were tested: two from the pseudomonas genre, *Pseudomonas fluorescens* (*P. fluorescens*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Serratia marcescens* (*S. marcescens*), a member of the family, *Enterobacteriaceae*. On biofilm formation, each species gave distinct, reproducible redox fingerprints with a detection limit of  $M. 4 \times 10^{-8}$  square wave adsorptive stripping voltammetry was used for detection. SEM and CV techniques were used to characterize the morphology and electrical conductivity of the modified electrode. In comparison to the bare screen-printed electrode, the modified electrode showed considerably higher performance and excellent sensitivity, along with a relatively fast analysis time. In work,<sup>50</sup> a two-dimensional (2D) Sb-modified screen-printed carbon nanofiber electrode (2D Sbexf-SPCNFE) was developed to improve the stripping voltammetric determination of Cd(II) and Pb(II), taking advantage of the synergistic effect between the two nanomaterials. After the experimental conditions were optimized, the 2D Sbexf-SPCNFE exhibited much better analytical parameters than the other assessed sensors. Analysis in 0.01 mol L@1 HCl (pH = 2) using 2D Sbexf-SPCNFE showed excellent linear behavior in the concentration range of 2.9–85.0  $\mu$ g L@1 and 0.3–82.0  $\mu$ g L@1 for Cd(II) and Pb(II), respectively. The limits of detection after 240 s deposition time for Cd(II) and Pb(II) were 0.9 and 0.1  $\mu$ g L@1, respectively, and sensitivities between 1.5 and 3 times higher than those displayed by SPCEbare, SPCNFEbare, and 2D Sbexf-SPCE were obtained. Finally, 2D Sbexf-SPCNFE was successfully applied to the determination of Cd(II) and Pb(II) traces in a certified estuary water sample. This paper<sup>51</sup> presents the validation of an electrochemical procedure for on-site Hg<sup>2+</sup>



ion determination in wastewater samples using a modified carbon screen-printed electrode (SPE) with a complexing polymeric film based on poly[2,2'-(ethane-1,2-diylbis((2-(azulen-2-ylamino)-2-oxoethyl)azanediyl)]diacetic acid) (polyL). Using metal ion accumulation in an open circuit followed by anodic stripping voltammetry, the SPE-polyL electrode presents a linear range of 20 to 150  $\mu\text{g/L}$ , with a limit of detection (LOD) = 6  $\mu\text{g/L}$ , limit of quantification (LOQ) = 20  $\mu\text{g/L}$ , and an average measurement uncertainty of 26% of mercury ions. The results obtained in situ and in the laboratory using the SPE-polyL modified electrode were compared with those obtained by atomic absorption spectrometry coupled with the cold vapor generation standardized method, with the average values indicating excellent recovery yields.

The method has high sensitivity, good reproducibility, expressiveness, and the possibility of automation for the experiment.

For detection in biological fluids, fentanyl can be measured in blood or urine to monitor abuse, confirm a diagnosis of poisoning, or assist in a forensic investigation of death. Commercially available immunoassays are often used as initial screening tests, whereas chromatographic methods are commonly used for confirmation and quantification. The Marquis color test can also be used to determine the presence of fentanyl. When formaldehyde and sulfuric acid are used, the solution turns purple when injected into opium drugs. It is expected that the concentrations of fentanyl in blood or plasma will be in the range of 0.3–3.0  $\mu\text{g/L}$  in people using the drug therapeutically, 1–10  $\mu\text{g/L}$  in people intoxicated, and 3–300  $\mu\text{g/L}$  in victims of acute overdose.<sup>52</sup> Paper atomization mass spectrometry may be useful for initial sample testing [20,53].

**2.6. Coulometric Method.** The coulometric method of analysis is used to determine the mass of a substance involved in an electrochemical and chemical reaction, to identify the products formed in this process, and to study the composition of poorly soluble and complex compounds, separation of metal phase analysis. However, for all coulometric methods, the following conditions are mandatory: the electrical conversion of the analyzed substance must proceed with almost 100% efficiency of the generation current (current output); the presence of a reliable method for determining the moment of completion of the electrochemical or chemical (in indirect coulometry) reactions; and accurate determination of the amount of electricity ( $Q$ ) that has passed through the cell until completion-controlled reaction.

Potentiometry is a method for determining the concentration of a substance and various physicochemical quantities based on the measurement of electrode potentials.

The disadvantages of potentiometric titration include not always achieving a quick determination of the potential solution after the addition of the titrant and the need to obtain a large number of samples during titration. To reduce the detection limits of electroanalytical methods, it is necessary to preconcentrate the diluted solution of the sample. For this purpose, some separation methods (e.g., liquid extraction) are applicable in which the interfering components are separated. These methods are lengthy and time-consuming; it is possible to lose part of the substance being determined in the process of concentration and introduce contaminants into the system to be analyzed. Therefore, it is more profitable to conduct preliminary accumulation in the system in which the measurements will be performed.

This principle is the basis of the inversion voltammetry method, which is discussed below. The substance being determined is concentrated electrochemically on the indicator electrode (forming an amalgam or film on the surface of the electrode), and then during the reverse (electrolytic) process, it is transferred to a solution. Thus, the substance under study in the electrode phase (at the electrode–solution interface) is in a significantly higher concentration than it was initially, and the sensitivity of the determination increases many times. Currently, voltammetry is the most often used for the analysis of environmental objects, which is an evolving method for analytical control. Modern studies provide data on more than 1000 methods of voltammetric determination.<sup>54</sup> Voltammetry with linearly varying potentials (direct voltammetry) is widely used in the analysis of inorganic and organic substances. Simultaneously, oxidation–reduction currents are recorded on voltammograms, the values of which depend on the concentrations of the substances in the solution. This method has limitations on the limits of detection of controlled substances (not less than  $10^{-5}$  M).

**2.7. Method of Inversion Voltammetry.** This method has significantly higher sensitivity.<sup>55–58</sup> The detection limits of the inversion voltammetry method for many substances are comparable to those of the most highly sensitive physicochemical methods ( $10^{-6}$  to  $10^{-10}$  M),<sup>3,59,60</sup> while the equipment used is relatively simple and small.<sup>61</sup> The low detection limit was achieved because of the preliminary electrochemical concentration of the detected substance on the indicator electrode.<sup>62</sup>

The detection limit of the inversion methods can be improved using catalytic reactions.<sup>63,64</sup> Here, the compound whose electrode reaction is catalyzed by the accumulated substance is in the solution, and its catalytic current is measured at the dissolution stage.<sup>65–67</sup> Using inversion methods, it is possible to successfully determine various elements in alloys, pure reagents, water, biological materials (in blood serum, urine), and food products.

Electrochemical inversion methods cannot, in principle, be used for continuous determinations because of the need for sequential stages of accumulation and dissolution; however, they are suitable for performing automatic serial analyzes during certain time intervals if suitable programming equipment is available.<sup>68,69</sup> Examples are software-controlled devices that use a stationary mercury drip electrode<sup>70–72</sup> and a rotating mercury film electrode.<sup>64–66</sup>

Voltammetric analysis has several advantages over other methods of analysis. Modern voltammetric analyzers allow the simultaneous determination of several components in one sample with fairly high sensitivity (up to  $10^{-8}$  M). Therefore, recently, the number of developments in analytical equipment using voltammetric methods (MVA) for the control of organic and inorganic substances has increased significantly in Europe and the USA.

When working with solid electrodes, the problem is the preparation of the electrode surface to obtain reproducible measurements. This disadvantage can be overcome by using disposable electrodes. They are associated with recent advances in the creation of new sensors, both chemical and biological. Similar to disposable medical instruments, they are discarded or disposed of after use. An example is planar electrodes made using screen printing technology, that is, printed using a printer. The cost of such electrodes is low since they can be manufactured in large quantities quickly enough and with small financial investments for the purchase of materials. To

implement this technology, minor changes in PC peripherals are required; as a rule, they are limited to changing the type of consumables, namely, carbon-containing ink and a ceramic- or plastic-based carrier, although special paper can be used. The ink composition completely determines the properties and characteristics of the planar electrode. The modifiers introduced into the ink composition affect the reversibility of the reactions and the magnitude of the response signal.

Recently, methods based on electrochemical sensors have been developed for the determination of organic and inorganic substances.<sup>73–75</sup> A large number of electrochemical sensors has been developed, particularly potentiometric sensors such as ion-selective electrodes and ion-selective field-effect transistors.

In practice, the stripping voltammetry method also requires careful sample preparation. This involves removing organic substances, which significantly affect the form of analytical voltammograms from the analyzed sample. On the other hand, the ability of organic substances to change the behavior of an electrochemical system containing cations of various metals can be used to analyze objects. An electrochemical method for the analysis of organic substances, multisensory stripping voltammetry, was developed at the Frumkin Institute of Physical Chemistry and Electrochemistry, the Russian Academy of Sciences, Moscow.<sup>64–66</sup> This method determines the change in the electrochemical activity of metal cations in a solution due to their interaction with organic substances. It was proposed to use metal cations with partially filled d-orbitals contained in the background electrolyte as a line of sensors, which can form complex compounds with alkaloids and, consequently, to form a multisensory test system.<sup>76</sup> These metals are clearly determined by stripping voltammetry, which allows the identification of various substances based on the analysis of characteristic changes in voltammetric curves resulting from the introduction of various alkaloids into the original test system. This opens the possibility of obtaining the required information on a single electrode. Thus, there is no need to use a set of several indicator electrodes whose number determines the number of informative parameters. The changes in the peaks of the dissolution currents of the metals are recorded on the obtained voltammogram, which can be determined for each metal of the test system separately or to integrally assess the change in the entire voltammogram. Measurements are performed on a single indicator electrode, which has a great advantage over multisensory methods that use a set of electrodes. Solving the task of identifying a specific organic substance by using this method requires comparison with a previously compiled database.

Earlier, for express diagnostics of biological objects using multisensory stripping voltammetry, we tested the method of early diagnosis of glaucoma, using blood serum.<sup>68</sup> Further studies have shown the working capacity and effectiveness of the method, in particular, when analyzing a number of ophthalmic drugs: Visomitin<sup>69</sup> and Lanosterol.<sup>70</sup> An increase in the strength of the complex present in the background increases the height of the peak of the metal dissolution current and, accordingly, decreases its width.<sup>71–73</sup> Assessment of the dynamics of changes in their concentration in the lacrimal fluid over time must determine the effective dosage of newly developed analgesic ophthalmic drugs. This study aimed to study the behavioral pharmacokinetics in the lacrimal fluid of an opioid drug, sevoflurane, in pediatric ophthalmology using multisensory stripping voltammetry in patients during strabismus correction surgery.

Previously, it was shown that the addition of a local anesthetic of the amide series (lidocaine, naropin, or chirocaine) to saline solution results in the immediate change of the CVA shape.<sup>74</sup> A novel electroactive composite based on silicotungstic acid (SiW), poly-*o*-phenylenediamine (PPD), and a reduced form of graphene oxide (RGO) was prepared by electrochemical synthesis on a planar screen-printed carbon electrode (SPCE) coated with GO. The new material was shown to have expressed the electrocatalytic activity as an example of the electrochemical behavior of the *p*-benzoquinone/hydroquinone redox couple on the RGO-PPD-SiW modified electrode. Unlike most composites containing heteropolyacid anions, RGO-PPD-SiW demonstrates its properties not only in an acid but also in a neutral saline solution. Potential cycling in a saline solution retains some CVA peaks observed in a 1 M H<sub>2</sub>SO<sub>4</sub> environment. The addition of a local anesthetic of the amide series (lidocaine, naropin, or chirocaine) to a saline solution changed the CVA shape immediately. Upon washing the electrode with double distilled water and filling with the initial saline solution or 1 M H<sub>2</sub>SO<sub>4</sub>, in each case, the corresponding CVA curve returns to the original shape, thus demonstrating the multiple usability of the composite electrode for analytical purposes by studying, for example, the presence of the said drugs in body fluids after their administration.

## 2.8. Conclusions of the Chapter.

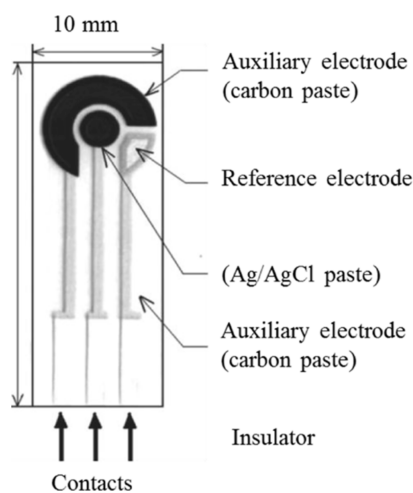
1. Based on the conducted analytical review, it is shown that electrochemical multisensory analysis in the “electronic language,” “electronic nose” format appears to be a promising way to improve the quality of analytical control of the alkaloid content in the study solution because, unlike currently used for identification and comparative analysis of alkaloids, drip chemical analysis, thin-layer chromatography, and mass spectroscopy, it is associated with difficulties in reproducing the electrochemical characteristics of sensors.
2. The advantages of the proposed multisensory analysis of organic substances by inversion voltammetry are that this method has several advantages, the main of which are the minimum number of stages of the analytical process, a low percentage of false-positive reactions, portability of equipment, a high degree of mobility, low mass of the test sample, and full automation of data processing and formation.

**2.9. Patients and Methods.** This article aimed to study the behavioral pharmacokinetics in the lacrimal fluid of the opioid drug sevoflurane in pediatric ophthalmology using multisensory stripping voltammetry in patients during strabismus correction surgery.

To select the effective dosage of various drugs, in particular analgesics, it is necessary to estimate the dynamic change in their concentrations in human body fluids, for example, in the lacrimal fluid during ophthalmic surgery.

A SPCE was reused; see Figure 1. The study drugs included lidocaine (20 mg/mL in glass ampoules by Pharmasyntez JSC, Russia), chirocaine (levobupivacaine hydrochloride, 7.5 mg/mL by Takeda NYCOMED, AS, Norway), naropin (7.5 mg/mL from AstraZeneca, Södertälje, Sweden), and fentanyl (50 mL from Moscow Endocrine Plant, Russia). The ampoules with sevoflurane, fentanyl, lidocaine, chirocaine, and naropin were opened immediately before the experiment.

This study employed multisensory stripping voltammetry to investigate the pharmacokinetic behavior of alkaloid-based



**Figure 1.** Planar electrode system.

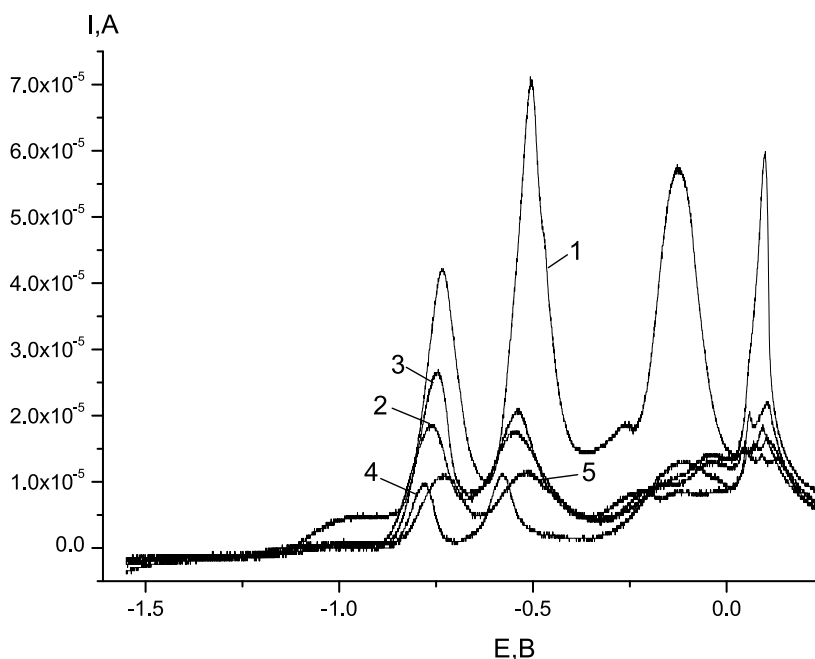
drugs (sevoflurane, fentanyl, naropin, chirocaine, and lidocaine) in the lacrimal fluid of ophthalmic patients undergoing strabismus correction surgery. In other words, this article presents examples of the dosage determination of local analgesic drugs, including sevoflurane, fentanyl, naropin, chirocaine, and lidocaine, used in ophthalmic operations through multisensory stripping voltammetry.

The study involved 30 patients aged 60–86 years with immature cataracts and mixed compensated glaucoma at stages I–III, equally distributed between men and women. The patients underwent phacoemulsification of the lens with intraocular lens implantation, and ten patients with concomitant glaucoma underwent combined surgery. The postoperative period was uneventful. Lacrimal fluid was collected from the patients using a sterile circular filter paper of 8 mm diameter before the operation and 5 and 10 min after anesthesia but before the incision (with instillation of an antibiotic solution,

0.25% chloramphenicol, after the last tear collection) to detect any solutions of anesthetic drugs in the tear. Each drug was administered retrobulbar and infrared (both according to the standard method) with a volume of 4 mL. The study was repeated in 18 patients to ensure the accuracy of the method, resulting in 108 samples.

**2.9.1. Monitoring Process.** The voltammograms obtained by the stripping voltammetry have a certain form (Figure 2) and are quite reproducible. These are the dependences of the current on the potential of the working electrode, which varies linearly over time. The recorded peaks correspond to the oxidation of different metals in the test system. The introduction of the analyzed organic substances into the test system changes the spectrum of the voltammograms. These changes are characteristic of each organic substance (or mixtures of substances), which allows their identification. The resulting voltammogram is divided into  $N$  sections, the number of which depends on the complexity of the system under study. This creates an  $N$ -dimensional image of the object.

During testing, 50  $\mu\text{L}$  of the test system was applied to the planar electrodes, and a background stripping voltammogram was recorded at a cathodic metal deposition potential of  $-1.55\text{ V}$  relative to the silver-chloride electrode, followed by a potential sweep up to  $0.3\text{ V}$ . Next, 50  $\mu\text{L}$  of a fresh test system solution and a disk of porous material (filter paper) with a particular drug applied to it in various concentrations were placed on the electrode, and the stripping voltammograms were again recorded. After a certain time (before the drug was administered and 5 or 10 min after its administration), the paper disk was removed from the conjunctival sac and placed on the electrode with a test system applied, and stripping voltammograms were recorded. Statistical processing of the results was performed by using Statistica 6.0 software. This study provides examples of the determination of the analgesic sevoflurane drug used for premedication before ophthalmic surgery using multisensory stripping voltammetry.



**Figure 2.** Stripping voltammograms of the test system in the presence of sevoflurane at different concentrations (%): (1)—0 (background), (2)— $0.125 \times 10^{-3}$ , (3)— $0.25 \times 10^{-3}$ , (4)— $0.375 \times 10^{-3}$ , and (5)— $0.5 \times 10^{-3}$  (on the electrode).



Sevoflurane provides a quick introduction to and exit from anesthesia. The depth of anesthesia can rapidly change depending on changes in sevoflurane's concentration in the inhaled mixture. The low solubility of sevoflurane in the blood results in a rapid increase in the alveolar concentration when administered under general anesthesia and a rapid decrease after cessation of inhalation. The ratio of the alveolar concentration at the end of inspiration and the concentration in the inhaled mixture 30 min after an inhalation of 5 min is 0.15.

Sevoflurane is indicated as an inhalation agent for the administration and maintenance of general anesthesia during surgical intervention in inpatient and outpatient settings in adults and children. Application of the substance sevoflurane 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane, (molecular formula  $C_4H_3F_7O$ ) (Figure 1) is a white crystalline powder. Its pharmacological action consists of an analgesic effect (opioid). Sevoflurane is indicated as an inhalation agent for the administration and/or maintenance of general anesthesia during surgical intervention in inpatient and outpatient settings in adults and children.

The study was conducted on children aged 2 years 4 months to 17 years who underwent surgery to correct strabismus. The postoperative period was uneventful. Before surgical interventions, children inhaled Sevoflurane (the active substance is sevoflurane) at a concentration of up to 8%, which usually provided the induction of general anesthesia in less than 2 min. The low solubility of sevoflurane in the blood results in a rapid increase in the alveolar concentration when anesthesia is induced and a rapid decrease after the cessation of inhalation. Rapid elimination of sevoflurane from the lungs minimized the drug's metabolism. An 8-mm disk made of pretreated porous material (filter paper, which was thoroughly washed in alcohol and distilled water and dried at 80 °C for 3 h) was placed in the conjunctival sac of the patient's eye to obtain samples of the lacrimal fluid.

For possible detection of solutions of anesthetic drugs in the tear after a certain time (before drug administration, 10 min, and 40 min after drug administration), the paper disk was removed from the conjunctival sac and placed on an electrode with the test system applied to it, and stripping voltammograms were recorded. There were 15 samples. The studies were conducted by using an electrochemical multisensory analyzer developed at the Institute of Physical Chemistry and Electrochemistry of the Russian Academy of Sciences. The developed device provides detection, preliminary identification, and comparative analysis of narcotic drugs and psychotropic substances and meets the following basic technical requirements:

- Volume of cells with a test system –1 mL;
- The detection limit of the analyzed substances in the sample is ( $10^{-6}$  to  $10^{-10}$ )M;
- The volume of the analyzed sample is (5–100)  $\mu$ L;
- Potential setting range  $\pm 2.5$  V;
- Error of setting the potential  $\pm 0.5\%$ ;
- Current measurement range  $\pm (1-200)$   $\mu$ A;
- Current measurement error  $\pm 0.5\%$ .

The software should provide the ability to conduct measurements in automated mode and implement algorithms for detection, preliminary identification, and comparative analysis of narcotic drugs and psychotropic substances.

The detection and identification of alkaloids were conducted on formed test systems using solutions of the following salts: nitrates of mercury, zinc, cadmium, lead, gallium, and cobalt.

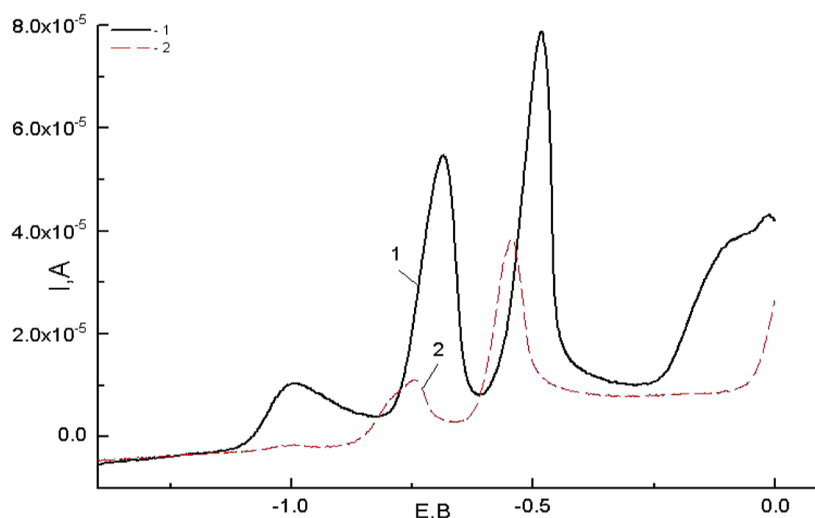
The studies were conducted on planar electrodes (Color-Electronics LLC), which are a polypropylene plate with applied working and auxiliary electrodes (carbon material) and a silver chloride reference electrode. The planar electrode diagram is shown in Figure 1. Because the planar electrodes are disposable, there was no need to prepare the surface of the indicator electrode.

**2.9.2. Statistical Analysis.** The introduction of the analyzed organic substances into the test system changes the spectrum of the voltammograms. These changes are characteristic of each organic substance (or mixtures of substances), which allows their identification. The resulting voltammogram is divided into N sections, the number of which depends on the complexity of the system under study. This creates an N-dimensional image of the object.

Statistical processing of the results was performed using Statistica 6.0 software.

A fundamentally new approach to solving the problem of analyzing volatile emissions is associated with the use of "electronic nose" devices [73,74]. The "electronic nose" direction as a whole developed on the basis of a number of fundamental principles related to the functioning of the olfactory system of mammals.<sup>73</sup> When using the "electronic nose" and "electronic tongue" devices, each analyzed substance corresponds to a certain characteristic response pattern of the multisensory system, which makes it possible to discriminate different substances (or mixtures of substances) by comparing their N-dimensional volumes times with a pregenerated database.<sup>73,74</sup> Currently, numerous commercial "electronic nose" and "electronic tongue" devices using sensor matrices of various types are described in the literature. A fairly complete list of "electronic nose, electronic tongue" models is presented in the literature.<sup>77</sup> A number of foreign and domestic companies have applied the developed analytical tools for assessing the quality of food products,<sup>78</sup> environmental monitoring,<sup>79</sup> and medical diagnostics.<sup>80</sup> In the latter case, diagnosis requires the satisfaction of several conditions. Typically, volatile biomarkers of disease states are present in exhaled air in very low concentrations. At the same time, in the responses of the sensory. The ditch is dominated by high concentrations of minor gases, such as CO<sub>2</sub> and water vapor. Therefore, to isolate a useful signal, a preliminary concentration of the sample is often required. Such operations increase both the time and the cost of analysis. It should be noted that there are many extraneous sources of volatile metabolites that can interfere with the "odor" image recorded by electronic nose devices, which in practice can be significant and can significantly complicate the process of diagnosing the disease. This study explores the fundamental possibility of using the "electronic tongue" and "electronic nose" formats to determine the dosage of anesthetics.

**2.9.3. Experimental Part.** The study used an electrochemical multisensor analyzer, as in the "electronic tongue" format, developed at the Institute of Physics and Chemistry of the Russian Academy of Sciences, Moscow. The test system (background electrolyte) consists of a solution of 0.05 M KCl, which contains the following cations of sensor metals: Zn<sup>2+</sup>, Cd<sup>2+</sup>, Pb<sup>2+</sup>, Cu<sup>2+</sup>, Co<sup>3+</sup>, Hg<sup>2+</sup>. Thus, a matrix of sensors is formed on a single electrode, ensuring the operation of the device in the "electronic tongue" and "electronic nose" formats. The measurements were performed on planar electrode systems (see Figure 1). The test\_system solution, which is also a background electrolyte, also served as a concentrator of volatile impurities. The initial voltammograms obtained in the test



**Figure 3.** Stripping voltammograms of the test system when exposed to sevoflurani at various concentrations (%): (1)—0 (background), (2)—10%.

system by stripping voltammetry have a certain appearance (Figure 2) and are well reproducible. The introduction of the analyzed organic substances into the test system changes the spectrum of the voltammograms. These changes are characteristic of each of the organic substances (or mixtures of substances), which allows their discrimination.

### 3. RESULTS

An electrolyte solution containing cations of a number of metals with the ability to form complex compounds with organic substances was used as the electrochemical test system:  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{3+}$ , and  $\text{Hg}^{2+}$ .<sup>64,65</sup> In our case, the matrix of sensors formed in this way on the indicator electrode ensured the functioning of the device in the electronic tongue format.<sup>65</sup> The voltammograms obtained by stripping voltammetry have a certain form (Figure 3, curve 1) and are clearly reproduced. They represent the dependence of the current on the potential of the working electrode, which changes linearly with time. The recorded peaks correspond to the oxidation of various metals in the test system. The introduction of the analyzed organic substances into the test system changes the spectrum of the voltammograms. These changes are characteristic of each organic substance (or mixtures of substances), which allows their identification. When metals are electrically dissolved from the electrode surface, the peak potentials of the dissolution currents determine the characteristics of the dissolving metal, and their amplitude depends on the amount of electrically dissolved metal. The composition of the background electrolytes noticeably affects both the magnitudes of the metal dissolution currents and the peak potentials.

An increase in the strength of the complex present in the background increases the height of the peak of the metal dissolution current and, accordingly, decreases its width.<sup>69</sup> As a result, the optimal composition of the test system solution was 0.05 M KCl containing the metal cations  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Co}^{2+}$ , and  $\text{Hg}^{2+}$  at a concentration of  $5 \times 10^{-5}$  M. During the tests, 50  $\mu\text{L}$  of the test system containing metal ions at the same concentrations ( $5 \times 10^{-5}$  M) was applied to the planar electrodes, and the background stripping voltammogram was recorded at the cathodic metal deposition potential of  $-1.55$  V relative to the silver-chloride electrode with subsequent potential development to 0.3 V. Then, 50  $\mu\text{L}$  of a fresh solution

of the test system and a disk made of a porous material (filter paper) coated with the drug in different concentrations were placed on the electrode, and the stripping voltammograms were recorded again.

The compositions of these drugs were close to the main active substance: these were local anesthetics, which belong to the pharmacological group of amides.<sup>76</sup>

**3.1. Effect of Sevoflurani on the Test System.** Figure 3 shows the results obtained for sevoflurani at various concentrations in vitro. It can be seen that in the presence of, the currents of metal ions included in the test system change to varying degrees depending on the concentration of sevoflurani with an increase in the concentration, the current of the mercury ion increases, while it decreases for other metals.

Since Sevoflurane is indicated as an inhalation agent and is a volatile ether, the study of volatile organic compounds in the “electronic nose” format is very relevant. In an “electronic nose” format, a blood serum sample with a volume of 50  $\mu\text{L}$  was applied to a disk ( $D = 8$  mm) of porous material (blue tape filter), placed in the cap of an Eppendorf tube ( $V = 2$  mL), and used as a source of “odor.” To concentrate volatile substances in the test\_si\_ solution, before the analysis, 100  $\mu\text{L}$  of test\_system\_ was injected into the test tube with the odor source. The tube was hermetically sealed and thermostated for 40 min at 40 °C. During this time, the test system sample is saturated with vapors of volatile metabolites from the test sample samples and is further examined by stripping voltammetry by analogy with the study statements in the “electronic language” format (see Table 1).

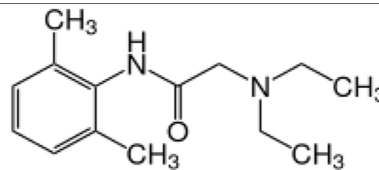
### 4. DISCUSSION

All data on the effects of sevoflurane, fentanyl, lidocaine, chirocaine, and naropin on the test system are summarized in Table 2. During the testing, 50  $\mu\text{L}$  of the test system was applied to the planar electrodes, and a background stripping voltammogram was recorded at a cathodic metal deposition potential of  $-1.55$  V relative to the silver-chloride electrode, followed by a potential sweep up to 0.3 V. Next, 50  $\mu\text{L}$  of a fresh test system solution and a disk of porous material (filter paper) with a particular drug applied to it in various concentrations were placed on the electrode, and the stripping voltammograms were again recorded. After a certain time (before the drug was

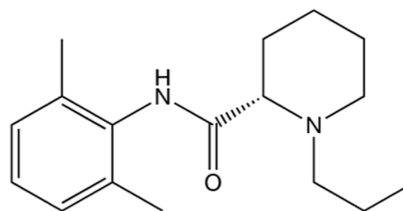


Table 1. Structure of Anesthetics

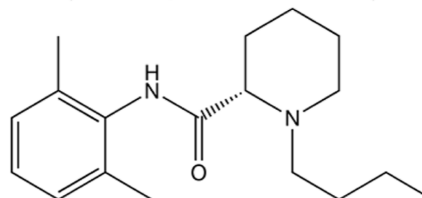
Lidocaine 2-(Diethylamino)-N-(2,6-dimethylphenyl) acetamide



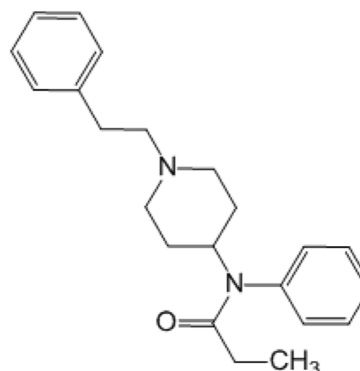
Naropin (levobupivacaine) (S)-N-(2,6-Dimethylphenyl)-1-propyl-2-piperidine carboxamide



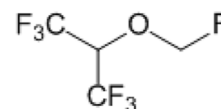
Chirocaine (ropivacaine) 2-(Diethylamino)-N-(2,6-dimethylphenyl) acetamide



Fentanyl (N-phenyl-N-[1-(2-phenylethyl)-4-piperidyl] propanamide molecular formula C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O)



Sevoflurane (Sevoflurani) 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane C<sub>4</sub>H<sub>3</sub>F<sub>7</sub>O



administered, and 5 or 10 min after its administration), the paper disk was removed from the conjunctival sac, placed on the electrode with a test system applied, and stripping voltammograms were recorded. As shown, in the presence of all of the anesthetics studied, the currents of the metal ions included in the test system changed to different extents depending on the anesthetic's concentration. As the concentration increased, so did the current of mercury ions, although the current decreased in other metals. The most remarkable change in the current of cadmium ions, namely, from 50 to 20  $\mu$ A, occurred in the range under study of concentrations of all the anesthetics studied.

Therefore, further experiments can be limited to study how patients' lacrimal fluid affects only those ions.

Sevoflurane's effect on the dissolution currents of metals in the test system can be explained by two phenomena: the ability of alkaloids to form complexes with metals and the adsorption of alkaloids on the electrode. Both phenomena complicate the electroreduction and electrooxidation of metals. Because the complexes may not be electroactive, their release of metals on the electrode is partly impeded. In this case, the number of electrodeposited metals on the electrode decreases, which subsequently decreases the electro-dissolution currents. The formation of metal–alkaloid complexes is influenced by various

**Table 2. Influence of the Anesthetics under Study on the Test System**

anesthetic	anesthetic concentration, %	peaks of the currents of dissolution of metals					
		Zn	Cd	Pb	Cu	Co	Hg
background		8	64	70.0	50.2	40.0	52.8
naropin	$0.125 \times 10^{-3}$	7	38	44	25	48	27
	$0.250 \times 10^{-3}$	8	42	42	28	28	59
	$0.375 \times 10^{-3}$	9	29	15	15	16	50
	$0.500 \times 10^{-3}$	16	20	16	20	20	90
chirocaine	$0.125 \times 10^{-3}$	6	35	43	24	45	25
	$0.250 \times 10^{-3}$	7	40	40	26	26	27
	$0.375 \times 10^{-3}$	8	25	14	14	15	50
	$0.500 \times 10^{-3}$	15	18	15	19	19	90
lidocaine	$0.125 \times 10^{-3}$	12	54	56	36	36	34
	$0.250 \times 10^{-3}$	8	52	43	21	21	16
	$0.375 \times 10^{-3}$	9	40	36	16	16	12
	$0.500 \times 10^{-3}$	6	20	31	12,5	12	80
fentanyl	$0.125 \times 10^{-3}$	23	39	62	49	48	35
	$0.250 \times 10^{-3}$	14	36	61	44	45	30
	$0.375 \times 10^{-3}$	15	34	67	43	44	25
	$0.500 \times 10^{-3}$	8	25	58	35	36	20
sevoflurani	$0.125 \times 10^{-3}$	22	40	59	45	30	76
	$0.250 \times 10^{-3}$	20	38	55	46	29	70
	$0.375 \times 10^{-3}$	19	35	56	44	30	69
	$0.500 \times 10^{-3}$	18	37	54	43	31	65

**Table 3. Effects of Anesthetics on the Lacrimal Fluid after Infraorbital Administration**

anesthetic	time of sampling	peaks of the currents of dissolution of metals					
		Zn	Cd	Pb	Cu	Co	Hg
background		8	64	70.0	50.2	40.0	52.8
naropin	before the administration of the drug	2	30	33	32	32	20
	5 min after administration	2	19	21	20	18	13
	10 min after administration	2	20	20	22	22	20
chirocaine	before the administration of the drug	4	26	31	23	21	22
	5 min after administration	3	23	23	26	26	20
	10 min after administration	2	23	33	25	26	23
lidocaine	before the administration of the drug	3	25	31	22	21	22
	5 min after administration	2	22	22	25	26	20
	10 min after administration	2	23	32	25	25	23
fentanyl	before the administration of the drug	33	71	71	31	30	25
	5 min after administration	22	50	50	20	21	22
	10 min after administration	20	21	21	20	21	23
sevoflurani	5 min after the administration	21	45	45	19	20	21
	10 min after the administration	19	20	19	18	19	20

factors, including the pH of the solution, the presence of various anions, and the metal concentration. The same conditions affect the dissolution currents of the electrodeposited metals. An important criterion for choosing the background electrolyte is the degree of influence of alkaloids on the peaks of the dissolution currents of metals in the test system.

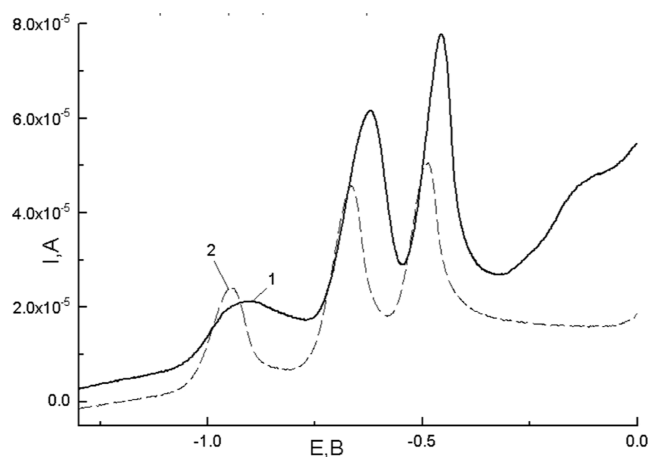
In the study range of sevoflurani concentrations, the most noticeable change was observed in the current of cobalt ions—from 120 to 65  $\mu\text{A}$ —and zinc ions—from 45 to 15  $\mu\text{A}$ . The change in the currents of cadmium and lead ions turned out to be somewhat smaller. Cadmium ions—from 40 to 38  $\mu\text{A}$ —and io lead ions—from 59 to 55  $\mu\text{A}$ . Consequently, it was sufficient to limit ourselves to studying the effect of lacrimal fluid only on these ions; the rest of the ions from the test system were excluded. As a result, the optimal composition of the test system solution was 0.05 M KCl containing the metal cations  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Co}^{2+}$ , and  $\text{Hg}^{2+}$  at a concentration of  $5 \times 10^{-5}$  M.

The data on the effect of sevoflurani on the test system are given in Table 3.

**4.1. Analysis of the Lacrimal Fluid of Patients after the Administration of Sevoflurani.** Figure 4 illustrates the effect of lacrimal fluid following the administration of Sevoflurani on the test system in electronic nose format.

The results of the analysis of patients' lacrimal fluid samples via multisensory stripping voltammetry are shown in Table 3. Based on the data obtained, it can be concluded that the most significant changes in the dissolution currents occurred for the cobalt and lead ions.

As a result, the optimal composition of the test system solution was 0.05 M KCl containing the metal cations  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Co}^{2+}$ , and  $\text{Hg}^{2+}$  at a concentration of  $5 \times 10^{-5}$  M. The sensor array formed in this manner on the indicator electrode provided the device operation in the electronic tongue and electronic nose format.<sup>70</sup> The voltammograms obtained by



**Figure 4.** Stripping voltammograms demonstrating the effect of the lacrimal fluid on the test system: (1) test system; (2) lacrimal fluid 10 min after sevoflurani administration.

stripping voltammetry had a certain form (Figure 2) and were readily reproducible. They also showed the current's dependence on the working electrode's potential, which varied linearly over time. In the voltammograms, the recorded peaks indicate oxidation of the different metals included in the test system.

The introduction of the analyzed organic substances into the test system induced changes in the spectrum of voltammograms, changes that were characteristic of each organic substance (or mixtures of substances), which allowed their identification. The resulting voltammogram is divided into  $N$  sections, the number of which depends on the complexity of the system under study. This creates an  $N$ -dimensional image of the object.

Statistical processing of the results was performed using Statistica 6.0 software.

## 5. CONCLUSIONS

A method has been developed that allows for electrochemical multisensory analysis of alkaloids in the mode of inversion voltammetry. An electrochemical multisensory test system has been developed that provides rapid analysis of alkaloids in the "electronic language" and "electronic nose" formats as format on a single electrode. A new approach to the analysis of alkaloids is presented based on the registration and quantitative accounting of the effect of complexation of organic ligands on a multisensory test system, which is a solution of metal salts with partially filled  $d$ -orbitals. An algorithm for identifying various alkaloids based on comparison with the database of the  $N$ -dimensional image of the object of study has been developed:

- 1) The study demonstrates the development of an electrochemical multisensory test system that provides expressed analysis of alkaloids (exemplified by sevoflurani) in the format "electronic nose" and "electronic language" format by stripping voltammetry on a single electrode. In the study range of sevoflurani concentrations, the most noticeable change was observed in the current of cobalt ions—from 120 to 65  $\mu\text{A}$ —and zinc ions—from 45 to 15  $\mu\text{A}$ . Consequently, it was sufficient to limit ourselves to studying the effect of lacrimal fluid only on these ions; the rest of the ions from the test system were excluded. As a result, the optimal composition of the test system solution was 0.05 M KCl containing the metal cations  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Co}^{2+}$ , and  $\text{Hg}^{2+}$  at a concentration of  $5 \times 10^{-5}$  M.

- 2) The studies were conducted using an electrochemical multisensor analyzer developed at the Institute of Physical Chemistry and Electrochemistry of the Russian Academy of Sciences. showed that the format "electronic nose" has the advantage of compared to the "electronic language" format in terms of methodological simplicity and in terms of wearing reliability of discrimination. The developed device provides detection, preliminary identification, and comparative analysis of narcotic drugs and psychotropic substances. The limit of detection of the analyzed substances in the sample is ( $10^{-6}$  to  $10^{-10}$ ) M. Potential setting range  $\pm 2.5$  V; potential setting error  $\pm 0.5\%$ . Current measurement range  $\pm (1-200)$   $\mu\text{A}$ ; current measurement error  $\pm 0.5\%$ . The software provides the ability to carry out measurements in an automated mode and implement algorithms for detection, preliminary identification, and comparative analysis of narcotic drugs and psychotropic substances.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

All data generated or analyzed during this study are included in the article text.

## ■ AUTHOR INFORMATION

### Corresponding Author

Irina Kolesnichenko — *Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Moscow 119071, Russian Federation*; [orcid.org/0009-0003-5369-5934](https://orcid.org/0009-0003-5369-5934); Email: [irinakol.phyche.ac.ru@mail.ru](mailto:irinakol.phyche.ac.ru@mail.ru)

Complete contact information is available at: <https://pubs.acs.org/10.1021/acsomega.3c03946>

### Notes

The author declares no competing financial interest.  
 Institutional Review Board Statement: All procedures involving patients conformed to the ethical standards of the Helsinki Declaration of 1964 and its subsequent amendments.  
 Informed Consent Statement: Informed consent was obtained from all participants included in the study.

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