Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

Development of Potentiometric Sensors for Selective Determination of Chlorpheniramine (CPA) with Comprehensive Greenness Assessment

Ram Ji Vishwakarma[1,*], Pratibha Singh[1,*], Shilpi Khurana[2], Keshav Kumar Saini[3] and Ravi Kant[4*]

[1]Department of Chemistry, K.S. Saket P.G. College, Ayodhya-224123, India
[2]Department of Chemistry, Deshbandhu College (University of Delhi), Kalkaji, New Delhi-110019, India
[3]Department of Chemistry, Dyal Singh College (University of Delhi). Lodhi Road, New Delhi-110003, India
[4]Department of Chemistry, Government Post Graduate College, Noida, G.B. Nagar-201301, India

(Received: 11 October 2024 Revised: 16 November 2024 Accepted: 10 December 2024)

KEYWORDS
Chlorpheniramine
Solid contact electrode
Ion selective membranes
β-Cyclodextrin
Greenness assessment

ABSTRACT:
Electrochemical devices, particularly ion-selective electrodes (ISEs), have emerged as robust green analytical instruments that are rapidly advancing and applicable in an increasing array of contexts. This research established and verified an innovative potentiometric sensing technique for the accurate identification of chlorpheniramine (CPA), even amidst its related pharmaceutical components. We compared the performance, advantages and disadvantages of two types of ion-selective electrodes (ISEs): traditional liquid-contact and new solid-contact configurations. The solid-contact electrodes were better than the old design in many ways. For example, they were better for the environment, they could do real-time analysis, they were portable, they were easy to throw away, they didn't need maintenance, they could be made smaller and they could work with modern microfabrication methods. The solid-state electrode was made of a nanocomposite membrane that used sulfobutylether-β-cyclodextrin as a supramolecular ionophore and multilayered carbon nanotubes as ion-to-electron transducers. The sensing mixture was easily applied in a single step by simply dropping it onto the surface of the custom-made copper electrodes. The sensors that were made worked well for measuring CPA in both its pure and pharmaceutical forms and had great analytical performance. IUPAC standards were used to judge their work and a statistical comparison with the official reference method showed that there were no major differences. We also used a number of evaluation tools to thoroughly check how green the proposed method was. These tools included the GAM (Green Analytical Method), the Analytical Eco-Scale, the GAPI (Green Analytical Procedure Index) and the AGREE, algorithm, which includes the twelve principles of green analytical chemistry. The RGB12 whiteness model finally showed that the method is overall sustainable, meaning it works well for both the environment and analysis.

1. Introduction

More and more people around the world have promised to use the ideas of green analytical chemistry (GAC) to come up with new ways to look at things in the last few years. The goal is to minimize adverse effects on health and the environment while maintaining the precision and efficacy of the analysis. Chemists still have a hard time finding the right balance between analytical performance and environmental sustainability [1,2].

One of the analytical methods that works well with GAC principles is ion-selective electrodes (ISEs). They are now very well-known as green choices. Potentiometric measurements are one of the least energy-intensive lab methods because they don't use any current. These methods don't require any sample pretreatment, use only a small amount of sample and create very little waste. Moreover, aqueous buffers and distilled water, prevalent solvents in ISE operations, are considered more environmentally friendly than organic solvents commonly employed in traditional analytical methods [3,4].

Liquid-contact ISEs used to have a sensing membrane between the sample and the filling solution inside. These electrodes have shown their analytical flexibility by being used in clinical, environmental, pharmaceutical and food analysis. People often use them to find blood electrolytes (Na^+, K^+, Ca^{2+}, Mg^{2+} and Li^+) [5,6], find toxic metals in the environment [7-10], check the quality of food [11] and help with drug quality control studies [12-14]. These old sensors work well, but they do have some problems. For example, ions can leak from the inner solution, the system performs poorly under high pressure

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

and it cannot measure in all directions. Additionally, it requires regular maintenance, has limited shelf life and cannot be easily miniaturized [15-17].

To address these challenges, researchers have turned to solid-contact ion-selective electrodes (SC-ISEs). Unlike traditional ISEs, SC-ISEs do not require an internal filling solution or a reference electrode. This innovation allows the fabrication of sensors that are more flexible, portable, low-maintenance and compatible with microfabricated and lab-on-a-chip systems. These advantages make SC-ISEs a promising next-generation technology for on-site and *in situ* analyses [18]. Selecting the appropriate electrode substrate material is a critical step in sensor fabrication. Commonly used metals for ion-selective membranes include gold, silver, platinum, copper, *etc*. [19,20]. Copper has attracted particular interest because it is inexpensive, widely available and compatible with advanced microfabrication techniques, such as printed circuit board (PCB) technology. Simple patterning methods like screen printing [21] and inkjet printing [22] can be used to create Cu electrodes on PCBs, offering a low-cost approach for producing miniaturized electrochemical devices. These devices can be readily integrated into portable, disposable or wearable sensors [23,24].

However, Cu-based electrodes have some problems, such as being unstable, having signals that drift and being sensitive to oxidation. A layer of water that forms at the interface between the conductive substrate and the ion-sensing membrane can also make it harder for ions to move from one place to another, which makes the electrode less reliable [25]. To lessen these effects, ion-to-electron transducer layers made of both ionic and electronic conductors have been added between the membrane and the solid substrate. To accomplish this, various nanomaterials have been employed, polymers with conductivity, such as graphene and carbon nanotubes [26-30].

The discovery of carbon nanotubes (CNTs) has revolutionized the use of carbon materials in electrochemistry [31]. Researchers have explored the use of both single-walled (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) for sensing applications. MWCNTs are particularly advantageous due to their superior chemical and thermal stability, ease of large-scale production and low cost. Their excellent electrical, optical and mechanical properties make them ideal for converting ions into electrons [18]. Being hydrophobic, MWCNTs prevent the formation of a water layer at the electrode interface, enhancing potential stability. In addition, they do not rely on redox reactions, minimizing undesired side processes that could compromise electrode performance [32,33]. Incorporating MWCNTs directly into the membrane matrix produces a single-piece composite electrode that is both easier to fabricate and mechanically stronger.

Crespo *et al*. [34] put forward an asymmetric capacitor model to elucidate the functioning of CNT-based SC-ISEs. This model shows that an electrical double layer forms at the interface between the solid and the contact. Similarly, Cuartero and his team gave more proof through spectroscopy that contacts that have been changed by CNTs act like capacitors [35]. The capacitive mechanism occurs when lipophilic anions adhere to the surface of the CNT layer, enhancing the stability and responsiveness of the electrode.

Chlorpheniramine (CPA), chemically designated as (*R*,*S*)-3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine, is a new-generation antihistamine commonly used for allergic conditions like conjunctivitis, hay fever, rhinitis, urticaria and [36,37]. Recent research indicates its efficacy against influenza viruses, suggesting its potential application in curtailing viral transmission during pandemics [38,39]. CPA can be administered independently or in conjunction with pseudoephedrine (PSE) and paracetamol (PAR) within multi-component pharmaceutical formulations, typically at a ratio of 1:15:100.

There is no documented potentiometric method for quantifying CAP, whether alone or in combination with other active constituents. This study aims to develop and validate a novel potentiometric technique for the selective, rapid and environmentally friendly quantification of CAP in both pure and tablet formulations, thereby avoiding the need for sample pretreatment. The proposed method consists of two primary steps: first, employing multiple liquid-contact electrodes (sensors 1–3) to identify optimal ion-selective membrane compositions; second, utilizing the best formulation to fabricate Cu-based solid-contact electrodes (sensors 4 and 5). The comparative study evaluates the performance of both configurations, their advantages and disadvantages and their limitations. A range of sustainability assessment tools was employed to conduct a detailed greenness evaluation of the developed method. These included the green analytical method (GAM)

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

[40], the analytical eco-scale [41], the green analytical procedure index (GAPI) [42] and the Analytical GREEnness (AGREE) algorithm [43], all of which align with the twelve principles of green analytical chemistry. Finally, the RGB12 model [44] was applied to assess the overall sustainability (white) of the analytical method.

2. Experimental

2.1. Materials and Apparatus

The study used only analytical-grade solvents and reagents. The sodium tetraphenylborate (NaTPB), high molecular weight PVC (polyvinyl chloride), bis(2-ethylhexyl) sebacate (BS), 2-hydroxypropyl-β-cyclodextrin (2-HPCD) and THF (tetrahydrofuran) were procured from Sigma-Aldrich USA, whereas disodium hydrogen phosphate and orthophosphoric acid potassium tetrakis-(4-chlorophenyl)borate (KTCPB) and 2-nitrophenyl-octyl ether (2-NPOE) from Fluka Chemie, Germany. The rest of the chemicals like potassium chloride(KCl), sodium hydroxide and hydrochloric acid were procured from SRL Chemicals, Mumbai, India. The double distilled water was used throughout the experiments.

Multi-walled carbon nanotubes (MWCNTs, ≥98% purity) measuring 3 to 6 μm long, 10 nm wide on outside and 4.5 nm wide on the inside. The pre-sensitized photo-resist-coated printed circuit boards (PCBs) and a UV lamp were used to make the electrodes.

For all potentiometric measurements, a Thermo Scientific Orion Ag/AgCl double-junction reference electrodewas used. A JENWAY 3510 pH/mV meter (Staffordshire, UK) and a WiseStir® magnetic stirrer were also procured. An AGREE software (v0.5, 2020) was used to conduct the green assessment of the method.

2.2. Reference Samples

Dr. Reddy Laboratory, Hyderabad, India generously provided the standards of chlorpheniramine (CPA) having the purity of 99.2 ± 0.9%. Brand tablets Cofton (Cipla, India) were purchased from the local pharmacy.

2.4. Standard Solutions

To prepare a stock solution of CPA (1×10^{-1} M), 1.017 g of pure CPA was dissolved in distilled water (pH 7.0) and subsequently diluted to a final volume of 25 mL in a volumetric flask. The working solutions (1×10^{-2} to 1×10^{-7} M) were prepared by mixing the stock solution with the same solvent over and over again.

2.5. Procedures

2.5.1. Fabrication of Liquid-Contact ISEs (Sensors 1-3)

Three types of ion-selective membranes were prepared for use in liquid-contact sensing systems. Sensor 1 was formulated using 66.60 wt.% bis(2-ethylhexyl)sebacate as the plasticizer, 33.17 wt.% PVC as the polymer matrix and 0.23 wt.% NaTPB as the ion-exchanger. Sensor 2 contained the same PVC content, but bis(2-ethylhexyl) sebacate was replaced with 66.60 wt.% 2-NPOE and KTCPB (0.23 wt.%) served as the ion-exchanger. For sensor 3, the composition of sensor 2 was modified by incorporating 0.63 wt.% 2-HPCD as the ionophore. Then 600 mg of each membrane formulation was dissolved in 6 mL of THF and cast the solutions into 5 cm glass Petri dishes. The films were allowed to dry overnight at RT, yielding transparent mem-branes, even at a thickness of approximately 0.1 mm.

2.5.2. Assembly of Liquid-Contact ISEs

Membrane disks approximately 8 mm in diameter were punched using a cork borer and attached to one end of PVC tubes with THF as the adhesive. The internal filling solution consisted of equal concentrations of 1×10^{-2} M CPA and 1×10^{-2} M KCl. A 1 mm Ag/AgCl wire was inserted to serve as the internal reference electrode. Prior to use, each sensor was conditioned for 24 h in a 1×10^{-2} M CPA solution.

Membrane disks approximately 8 mm in diameter were prepared using a cork borer and affixed to one end of PVC tubes with THF as the adhesive. The internal filling solution comprised equal concentrations of 1×10^{-2} M CPA and 1×10^{-2} M KCl. A 1 mm Ag/AgCl wire was placed inside the tube to function as the internal reference electrode. Prior to use, the sensors were conditioned for 24 h in a 1×10^{-2} M CPA solution.

The pattern of the electrodes was printed on clear film using a high-resolution laser printer. After that, the electrode was put over the presensitized PCB and the whole thing was exposed to UV light (365 nm) for 30 sec. We used 0.25 M NaOH to develop the exposed photoresist areas and get rid of the ones that weren't protected. Then, copper was etched with 1 M ammonium persulfate at 40 °C for 10 to 15 min while stirring. The

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

remaining portion was taken off with acetone and the surface of the electrode was cleaned in order with isopropanol, glacial acetic acid and distilled water.

2.5.4. Solid-Contact ISEs

The membrane cocktail for sensor 4 consisted of 33.17 wt.% PVC, 66.60 wt.% 2-NPOE, 0.23 wt.% KTCPB, 0.63 wt.% 2-HPCD and 0.5 wt.% MWCNTs. All components were combined in 6 mL of THF, sonicated for 30 min and subsequently mixed again to ensure homogeneity. A 10 µL aliquot of the resulting solution was then deposited onto the surface of copper electrode and left to dry overnight to allow complete solvent evaporation. This simplified fabrication approach incorporates MWCNTs directly into the sensing membrane, producing a solid-contact electrode without the need for an intermediate transducing layer [45]. For comparison, a similar membrane formulation was prepared for sensor 5, but without the addition of MWCNTs, in order to evaluate the influence of the transducer material on potential stability. Both electrodes were conditioned in a 1×10^{-2} M CPA solution for 24 h prior to calibration.

2.5.5. Fabrication of sensors

Each electrode had a double-junction Ag/AgCl reference electrode attached to it and the electrodes were put in CPA standard solutions ($1 \times 10^{-7} – 1 \times 10^{-2}$ M). While being stirred, the potential was allowed to stabilize and readings were taken within ±1 mV. Calibration curves were constructed by plotting the emf (mV) as a function of log[CPA]. The slope and linear regression equation were determined in accordance with IUPAC recommendations [46]. The response time was defined as the period required for the potential to stabilize within ±1 mV following a tenfold increase in analyte concentration.

2.5.6. Effect of pH variations

The pH was adjusted using dilute HCl or NaOH to evaluate the response of each electrode over the pH range of 2–10. The electrode potential was plotted as a function of pH to identify the optimal range for accurate CPA measurements.

2.5.7. Selectivity studies

To assess sensor selectivity, the potential responses toward CPA were measured in the presence of common pharmaceutical excipients and co-formulated drugs. Selectivity coefficients ($K^{(pot)}_{CPA,Int}$) were determined using the separate solutions method described by IUPAC [46]. In this approach, E_1 and E_2 represent the potentials of CPA and the interfering ion, respectively; S is the slope of the calibration curve; z_{CPA} and z_{Int} are the corresponding ionic charges; and a_{CPA} denotes the activity of CPA:

$$\log(K^{pot}_{CPA,Int}) = \frac{E_2 - E_1}{S} + \left(1 - \frac{Z_{CPA}}{Z_{Int}}\right)\log \alpha CPA$$

2.5.8. Potentiometric measurements of CPA in tablets

Cofton tablets were weighed, ground and homogenized. An amount of the powdered sample equivalent to the labelled content was transferred to a 25 mL volumetric flask, to which 1.0×10^{-3} M CPA was added and the mixture was diluted to the mark with distilled water (pH 7). After appropriate serial dilutions, the resulting solution was analyzed by immersing the prepared electrodes along with an Ag/AgCl reference electrode. The recorded potentials were then applied to the calibration equation to determine the CPA content in the sample.

3. Result and discussion

3.1. Physico-chemical parameters of ISEs

The research began with preparing liquid-contact ISEs (sensors 1–3), after which the optimum membrane formulation was applied to microfabricated copper-based solid-contact electrodes (sensors 4 and 5). All sensors showed Nernstian responses, with the MWCNT-modified electrode (sensor 4) achieving the steepest slope and offering advantages in response time, stability and miniaturization.

PVC was used as the membrane matrix to ensure mechanical stability and efficient immobilization of ion-association complexes. Membrane composition was tailored to the cationic nature of carbinoxamine maleate (CPA; log P 3.27, pK_a 8.7), employing NaTPB and KTCPB as ion exchangers. Conditioning in 1.0×10^{-2} M CPA promoted effective ion pairing.

Plasticizer selection significantly affected sensor performance. BS and 2-NPOE yielded slopes of 40.0 ± 1.8 and 51.3 ± 1.3 mV decade^{-1}, respectively. Incorporation of 2-hydroxypropyl-β-cyclodextrin (2-HPCD) in sensor 3 enhanced both sensitivity and selectivity through CPA inclusion-complex formation. This optimized formulation was subsequently used for the solid-contact ISEs.

3.1.2. MWCNTs working in solid-contact ISEs

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

Solid-contact ion-selective electrodes (ISEs) offer compact design, easy storage and compatibility with modern miniaturized analytical systems, including lab-on-a-chip devices and *in situ* biomedical sensors. Incorporating an ion-to-electron transducing layer eliminates the blocked interface typically formed between the ion-sensing membrane (ISM) and the underlying electronic conductor in traditional ISE architectures.

The potentiometric response of solid-contact electrodes is governed by the interfacial capacitance established at the ISM/solid-contact junction. The magnitude and stability of this capacitance depend on the physical and electrochemical characteristics of the transducer material, which functions as an asymmetric capacitor capable of supporting charge–discharge processes under the low current conditions inherent to potentiometric measurements.

Carbon nanotubes (CNTs) are particularly effective transducers due to their strong hydrophobicity, high double-layer capacitance and absence of redox activity attributes that collectively enhance signal stability and operational reproducibility. In this study, MWCNTs were integrated as the transducing component to facilitate efficient ion-to-electron conversion at the ISM/solid-contact interface. The electrical double layer formed at this boundary, involving charge carriers in the solid-contact material and mobile ions within the membrane phase, significantly improved potential stability and response precision.

To evaluate the role of MWCNTs, the performance of a single-piece ISE containing dispersed MWCNTs was compared with a control sensor lacking a transducer layer. Unlike conventional multilayer designs, the single-piece configuration incorporates MWCNTs directly into the membrane cocktail, simplifying fabrication. The control electrode exhibited pronounced potential drift and instability, likely due to water-layer formation at the interface. In contrast, the MWCNT-based sensor showed markedly improved stability, minimal drift, extended operational lifetime and an enhanced Nernstian slope (55.2 ± 0.3 mV dec.$^{-1}$) relative to the control (50.3 ± 0.7 mV dec.$^{-1}$). A summary of the performance characteristics for all fabricated sensors is shown in Table-1.

3.1.3. Characterization of MWCNTs (sensor 4)

Electrochemical sensors working

We evaluated the electrochemical behaviour of all fabricated ion-selective electrodes in accordance with IUPAC recommendations [46]. A summary of the principal calibration parameters including linearity, precision and mean accuracy is presented in Table-1. Calibration graphs were prepared by plotting the electrode potential (mV) against the logarithm of CPA concentration under optimized experimental conditions.

As illustrated in Figs. 1 and 2, all sensors exhibited highly linear responses within the concentration range of 1.0×10^{-5} to 1.0×10^{-2} mol/L. The slopes obtained from the linear segments of these calibration curves deviated from the theoretical Nernstian slope of 60 mV/dec., which is expected since electrode potentials depend on ionic activity

Table-1
Response characteristics of the investigated sensors and the validation parameters of the response

Parameters	Liquid contact			Solid contact	
	Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5
Slope (mV/ decade) ± SD[a]	40.0 ± 1.8	51.3 ± 1.3	53.1 ± 0.8	55.2 ± 0.3	50.3 ± 0.7
Intercept (mV) ± SD[a]	243.7 ± 6.0	281.0 ± 5.6	292.9 ± 4.1	314.6 ± 1.5	205.4 ± 2.6
Correlation coefficient (r)	0.9991	0.9998	0.9998	0.9996	0.9995
Concentration range (mol/L)	1.0×10^{-5}–1.0×10^{-2}	1.0×10^{-5}–1.0×10^{-2}	1.0×10^{-5}–1.0×10^{-2}	1.0×10^{-5}–1.0×10^{-2}	1.0×10^{-5}–1.0×10^{-2}
Working pH range	4–7	4–7	4–7	4–7	4–7
Repeatability precision (RSD %)[b]	1.3	0.9	0.7	0.9	1.4
Intermediate precision (RSD %)[c]	1.8	1.2	1.0	1.3	1.7
LOD (mol/L)[d]	1.1×10-5	1.0×10-5	9.7×10-6	3.2×10-6	5.0×10-6
Response time (sec.)	15 ± 7	15 ± 7	15 ± 5	5 ± 2	10 ± 5
Life span (weeks)	3	3	3	8	4

[a]Average of three determinations. [b]Repeatability precision (intra-day) (n = 9), average of three different concentrations of three replicate each (1.0×10^{-3}, 1.0×10^{-4} and 1.0×10^{-5} mol/ L) being analyzed three times within the day. [c]Intermediate precision (inter-day) (n = 9), average of three different concentrations of three replicate each (1.0×10^{-3}, 1.0×10^{-4} and 1.0×10^{-5} mol/ L) being analyzed three times on three consecutive days. [d]LOD (Limit of detection) according to the IUPAC definition, measured by intersection of the extrapolated arms of non-responsive and the Nernstian segments of the calibration plot.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

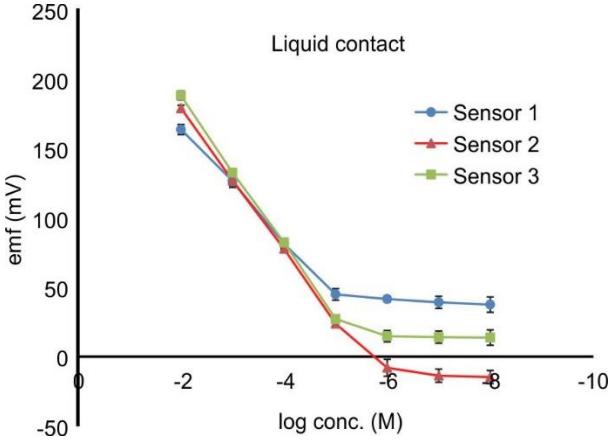

Fig. 1. Electrochemical potential (mV) *vs*. log CPA concentration measured by sensors 1–3. Data expressed as mean ± standard deviation (n = 3) for each concentration

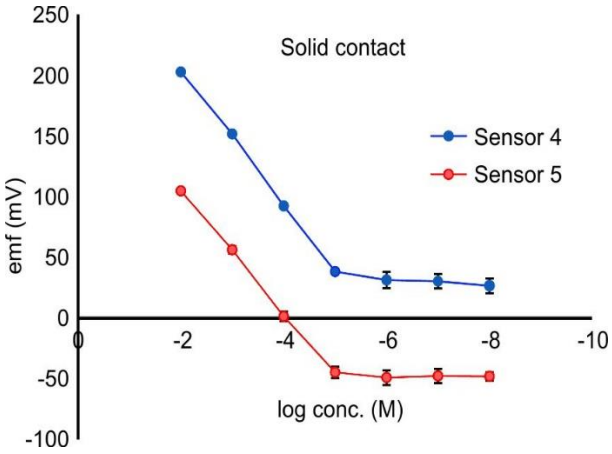

Fig. 2. Electrochemical potential (mV) *versus* log [CPA] measured by sensors 4 and 5. Data expressed as mean ± standard deviation (n = 3) for each concentration

rather than absolute concentration. The average slopes for sensors 1 through 5 were 40.0 ± 1.8, 51.3 ± 1.3, 53.1 ± 0.8, 55.2 ± 0.3 and 50.3 ± 0.7 mV/decade, respectively.

All prepared electrodes demonstrated stable and reproducible performance. Day-to-day variations in potential were minimal, remaining within ±2 mV. After extended use, the calibration slopes for sensors 1–5 were maintained for approximately 3, 3, 3, 8 and 4 weeks, respectively. Notably, solid-contact ISEs displayed superior longevity compared with their liquid-contact counterparts. This enhanced durability is attributed to the strong retention of ion exchanger species within the membrane matrix, which minimizes leaching into the sample solution and helps preserve sensor sensitivity over time.

3.3. Effect of pH

The effect of pH on the potentiometric response of the developed electrodes were investigated to identify the conditions that yield the most reliable analytical results. A 1.0 × 10^{-3} mol/L CPA solution was used and the potential of the optimized sensor was monitored across a pH range of 2–10. The resulting potential–pH profile (Fig. 3) indicates that the electrode signal remained essentially constant between pH 4 and 7, confirming that the sensors perform optimally within this interval. In this pH region, CPA predominantly exists in its ionized form, which promotes effective interaction with the ion-selective membrane. Beyond these limits, the recorded potential gradually decreased, likely due to changes in the drug's protonation state or competition from H^+ or OH^- ions under strongly acidic or alkaline conditions.

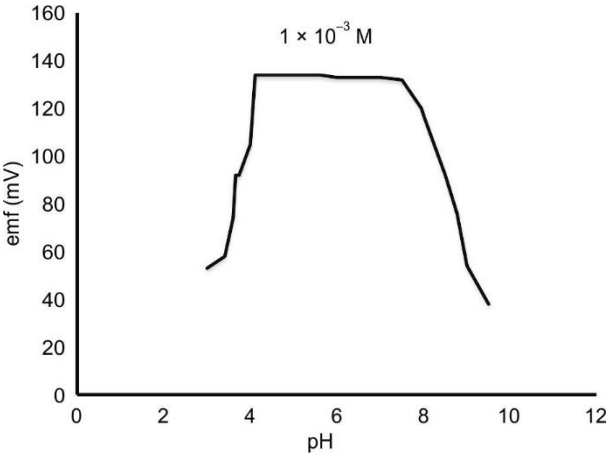

Fig. 3. Plot of pptimal pH Range (4–7) for CPA detection with sensor-3

3.4. Selectivity studies

The selectivity of the fabricated electrodes were assessed by monitoring their responses in the presence of common pharmaceutical excipients, co-formulated drugs and physiologically relevant inorganic cations. The potentiometric selectivity coefficients listed in Table-2 indicate that the sensors exhibited strong preference for CPA, with negligible interference from the examined species.

Upon exposure to CPA, hydrophilic compounds such as pseudoephedrine (PSE) and paracetamol (PAR), along with typical inorganic ions (K^+, Na^+, Mg^{2+}, Ca^{2+}), were unable to displace CPA from the membrane phase. This pronounced selectivity can be attributed to differences in

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

Table-2
Potentiometric selectivity coefficients ($K^{pot}_{CRA,Int}$) of the suggested sensors calculated using the separate solution method

Interferent (10^{-3} M)	Selectivity coefficients[a]				
	Liquid contact			Solid contact	
	Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5
PSE	3.0×10^{-2}	1.2×10^{-2}	9.7×10^{-3}	3.0×10^{-3}	3.7×10^{-3}
PAR	7.8×10^{-3}	2.0×10^{-3}	5.0×10^{-3}	1.1×10^{-3}	2.0×10^{-3}
KCl	5.6×10^{-3}	2.9×10^{-3}	2.1×10^{-3}	7.0×10^{-4}	7.8×10^{-4}
NaCl	5.3×10^{-3}	2.7×10^{-3}	2.2×10^{-3}	9.1×10^{-4}	8.1×10^{-4}
$CaCl_2$	7.8×10^{-3}	1.7×10^{-3}	3.0×10^{-4}	7.3×10^{-4}	8.9×10^{-4}
$MgCl_2$	7.4×10^{-3}	1.9×10^{-3}	2.2×10^{-4}	6.9×10^{-4}	6.8×10^{-4}

[a]Each value is the average of three determinations.

ionic size, hydration energy and lipophilicity factors that hinder the penetration of competing ions into the hydrophobic sensing membrane.

CPA has a log P value of 3.27, making it substantially more lipophilic and partitions more readily into the membrane and interacts more strongly with the ion-exchange sites. Calibration curves obtained for the potential interfering ions using the optimized electrode (sensor 4) further confirmed its high selectivity towards CPA.

3.5. Potentiometric measurement of CPA in pharmaceutical dosage form

The fabricated ion-selective electrodes were effectively applied for the direct determination of carbinoxamine maleate in its combined tablet dosage form, eliminating the need for any prior sample treatment or separation steps. The analytical results confirmed that neither the accompanying active ingredients nor the excipients interfered with the measurement of CPA, thereby demonstrating the high specificity and suitability of the sensors for routine pharmaceutical analysis.

The liquid-contact electrodes had the following percentage recoveries:

At 1.0×10^{-3} M and 1.0×10^{-4} M, Sensor 1 had a range of 98.7 ± 1.6 % (n = 3) and 99.2 ± 1.8 % (n = 3).

Sensor 2: 99.3 ± 0.5 % (n = 3) and 98.9 ± 0.2 % (n = 3).

Sensor 3: 99.9 ± 0.6 % (n = 3) and 101.1 ± 0.4 % (n = 3).

For the solid electrodes:

Sensor 4: 99.6 ± 0.7 % (n = 3) and 100.3 ± 0.5 % (n = 3).

Sensor 5: 99.2 ± 1.3 % (n = 3) and 100.8 ± 1.7 % (n = 3).

The results in Table-3 show that the proposed potentiometric method is accurate, precise and reproducible. The recoveries are within the acceptable analytical parameters, indicating that the developed sensors are suitable for conducting routine analyses of CPA in pharmaceutical dosage forms without necessitating complex or time-consuming sample preparation procedures.

3.6. Validation of the Method

The potentiometric performance characteristics of the constructed sensors were validated according to the standards set by IUPAC (International Union of Pure and Applied Chemistry) [46]. Table-1 displays the results obtained, along with all the significant validation parameters.

3.6.1. Linearity and Range

To assess linearity, four concentrations of CPA were analyzed in triplicate using the prepared electrodes. Calibration curves for each sensor were generated by plotting the measured potentials (mV) against the negative logarithm of CPA concentration, as illustrated in Figs. 1 and 2.

Both the liquid-contact and solid-contact electrodes exhibited a clear linear relationship between potential and logarithmic concentration over the range of 1.0×10^{-5} to 1.0×10^{-2} mol/L. The regression equations for all sensors

Table-3
Application of the proposed sensors in pharmaceutical formulation

Pharmaceutical formulation	Concentration (mol/L)	Recovery % ± SD[a]				
		Liquid contact			Solid contact	
		Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5
Cofton tablets	1×10^{-3}	98.7 ± 1.6	99.3 ± 0.5	99.9 ± 0.6	99.6 ± 0.7	99.2 ± 1.3
	1×10^{-4}	99.2 ± 1.8	98.9 ± 0.2	101.1 ± 0.4	100.3 ± 0.5	100.8 ± 1.7

[a]The recovery percentages are the average of three determinations.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

showed excellent linearity, with correlation coefficients of 0.9991, 0.9998, 0.9998, 0.9996 and 0.9995 for sensors 1 through 5, respectively. These values confirm the strong dependence of the electrode potential on the activity of the analyte.

3.6.2. Rightness

Accuracy indicates the closeness of measured values to the true or accepted concentrations. To assess this parameter, all fabricated electrodes were employed to analyze three CPA concentrations *viz*. 5.0×10^{-5}, 5.0×10^{-4} and 5.0×10^{-3} mol/L, each measured in triplicate. The corresponding concentrations were calculated using the appropriate calibration equations and the mean percentage recoveries were determined.

Liquid-contact electrodes produced recoveries between 98.9% and 99.7%, while solid-contact electrodes showed recoveries of 99.6 ± 1.1% to 99.9 ± 0.9%. The results in Table-4 confirmed that the proposed potentiometric sensors deliver highly accurate and reliable measurements.

3.6.3. Exactness

3.6.3.1. Repeatability (Accuracy Within a Day)

Repeatability was evaluated by measuring CPA solutions at concentrations of 1.0×10^{-5}, 1.0×10^{-4} and 1.0×10^{-3} mol/L on the same day for each type of electrode. The recovered concentrations were calculated using the corresponding calibration equations and the percentage recovery, standard deviation (SD) and relative standard deviation (%RSD) were determined.

For liquid-contact electrodes, intra-day %RSD values ranged from 0.7% to 1.3%, while solid-contact electrodes exhibited %RSD values between 0.9% and 1.4% (Table-1). These results indicate that the sensors provide highly consistent measurements and can be reused reliably.

3.6.3.2. Accuracy (Inter-Day)

Intermediate precision was evaluated by measuring three concentrations of CPA in triplicate over three consecutive days using all proposed sensors. As shown in Table-1, the inter-day %RSD values ranged from 1.0% to 1.8% for liquid-contact electrodes and from 1.3% to 1.7% for solid-contact electrodes. Since all values remained below 2.0%, the results demonstrate that the method is highly accurate and maintains stability over time.

3.6.4. Limit of Detection (LOD)

The limit of detection (LOD) represents the lowest concentration of CPA that the electrode system can reliably identify, without requiring exact quantification. Following IUPAC guidelines, the LOD was determined from the intersection between the non-responsive (low-concentration) region and the linear Nernstian segment of the calibration curve [46].

The following LOD values were found:

For liquid-contact sensors, the values are 1.1×10^{-5} M (sensor 1), 1.0×10^{-5} M (sensor 2) and 9.7×10^{-5} M (sensor 3).

Sensors for solid contact: 3.2×10^{-6} M (sensor 4) and 5.0×10^{-6} M (sensor 5).

The solid-contact ISEs exhibited higher sensitivity, enabling detection of analytes at lower concentrations. This improvement is attributed to the absence of an internal filling solution, which in liquid-contact electrodes can slow ion transfer from the membrane to the sample, particularly at low analyte levels. Overall, solid-contact electrodes demonstrated superior analytical performance compared with their liquid-contact counterparts.

3.7. Statistical analysis

The proposed potentiometric method's analytical effectiveness was statistically assessed in comparison to the official

Table-4
Accuracy of the proposed method for the determination of CPA in pure powder

CPA concentration (M)	Recovery %[a]				
	Liquid contact			Solid contact	
	Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5
5.0×10^{-5}	97.0	99.0	99.3	100.9	100.8
5.0×10^{-4}	99.7	99.1	100.0	99.1	98.6
5.0×10^{-3}	100.0	100.4	100.0	99.8	99.3
Mean ± SD	98.9 ± 1.7	99.5 ± 0.8	99.7 ± 0.4	99.9 ± 0.9	99.6 ± 1.1
%RSD	1.7	0.8	0.4	0.9	1.1

[a]Average of three determinations.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

reference procedure [36] for quantifying the examined compounds in their pure powdered forms. The Student's t-test and the F-test was used to check the results for accuracy and precision, respectively. The calculated t and F values (Table-5) were inferior to the theoretical values, indicating no significant difference between the results derived from the proposed and official methods at a 95% confidence level.

A one-way analysis of variance (ANOVA) was conducted to examine potential differences both between and within the applied methods. The calculated F values (Table-6) were consistently lower than the corresponding critical values, indicating no statistically significant differences in accuracy or precision between the proposed and official methods. These findings confirm that the developed potentiometric method produces results comparable to the reference procedure, while offering the advantages of being simpler, faster and more environmentally friendly.

3.8. Evaluation of the developed method's environmental friendliness

A comprehensive greenness assessment was performed using several standardized evaluation tools to ensure that the newly developed analytical method aligns with the principles of green and sustainable chemistry. While the electrochemical methods are generally considered environmentally friendly due to minimal sample preparation and low solvent use, objective verification is essential.

The Green Analytical Method (GAM), Analytical Eco-Scale, Green Analytical Procedure Index (GAPI), Analytical GREEnness (AGREE), algorithm and the recent RGB12 model were applied to evaluate various aspects of environmental impact, long-term sustainability and analytical efficiency. Relevant acceptance criteria were used to construct a detailed green profile for the proposed potentiometric method, allowing a systematic assessment of its eco-efficiency.

The results from all applied evaluation models confirmed that the method complies with the core principles of both GAC (Green Analytical Chemistry) and WAC (White Analytical Chemistry). As summarized in Table-7 and Fig. 4, the method demonstrates strong environmental compati-bility and sustainability, highlighting its suitability as a green analytical approach for routine pharmaceutical analysis.

4. Conclusion

The present work explored the feasibility of potentiometric techniques as eco-friendly analytical tools in accordance with the criteria of Green Analytical Chemistry (GAC). A comparative evaluation of two electrode configurations *e.g.* traditional liquid-contact and modern solid-contact ISEs was conducted, introducing the first potentiometric system for the selective quantification of chlorpheniramine (CPA). The study began with conventional liquid-contact electrodes and advanced to copper-based solid-contact sensors.

Through careful optimization of the membrane composition and design, a solid-contact sensor incorporating multi-walled carbon nanotubes

Table-5
Statistical analysis of the results obtained by the proposed sensors for the determination of CPA in its pure powdered form and the official method

Items	Liquid contact			Solid contact		Official method for CPA [24][a]
	Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5	
Mean	99.93	99.98	100.01	100.02	99.90	99.23
SD	0.89	0.64	0.48	1.37	1.97	0.88
Variance	0.79	0.41	0.23	1.86	3.87	0.77
n	4	4	4	4	4	6
Student's t test[b]	1.24 (2.306)	1.455 (2.306)	1.597 (2.306)	1.132 (2.306)	0.748 (2.306)	
F test[b]	1.02 (5.41)	1.90 (9.01)	3.36 (9.01)	2.42 (5.41)	5.03 (5.41)	

[a]USP official methods for CPA is non-aqueous titration with 0.1 M perchloric acid using crystal violet as indicator until endpoint a blue green color is obtained. [b]The figures in parenthesis are the corresponding theoretical values at (P=0.05).

Table-6
ANOVA (single factor) for comparison of the results of the proposed sensors and the official method for determination of CPAin pure powdered form

Source of variation	Sum of squares	DF	Mean square	F value	F crit[a]
Between exp.	2.559	5	0.512	0.405	2.711
Within exp.	25.301	20	1.265		
Total	27.860	25			

[a]Tabulated value for F at p equals 0.05.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

Table-7
Assigning penalty points to calculate the analytical Eco-Scale for the proposed method

Eco-scale hazard	Penalty points
Reagents	
Tetrahydrofuran (less than 10 mL)	6
PVC (less than 10 g)	1
Potassium *tetrakis*(4-chlorophenyl) borate (less than 10 g)	1
2-Hydroxypropyl cyclodextrin (Less than 10 g)	1
Water	0
Instruments	
Energy consumption	0
Occupational hazard	0
Waste	3
Waste amount (1-10 g or mL)	
Waste treatment	
(No treatment)	3
Total penalty points (PP)	15
Eco-Scale total score[a,b]	85

[a]Analytical Eco-Scale total score = 100- total penalty points.
[b]If the score is > 75, it represents excellent green method; If the score is > 50, it represents acceptable green method; If the score is less than 50, it represents inadequate green method.

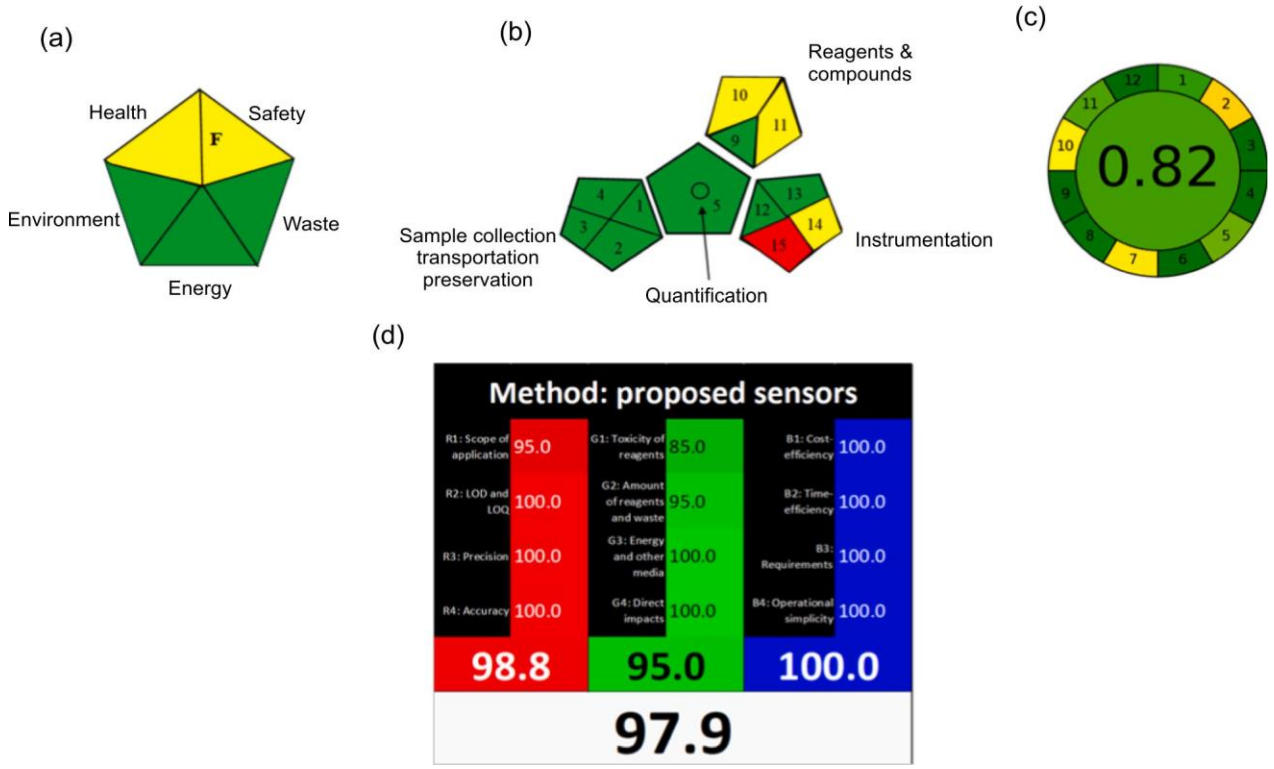

Fig. 4. Greenness metrics of the proposed method assessed by GAM, GAPI, AGREE, and RGB12

(MWCNTs) was developed. This design effectively addressed a major limitation of solid-contact electrodes: signal instability and potential drift over time. Structural and morphological analyses of the nanocomposite membranes confirmed successful integration of the transducing material and its role in enhancing signal stability.

The solid-contact sensors outperformed traditional liquid-contact electrodes, offering faster response times, greater durability, higher selectivity and lower detection limits. Moreover, the solid-contact design overcame several limitations of liquid-contact systems, including ion leakage, restricted miniaturization, orientation constraints and incompatibility with high-pressure or

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

wearable applications. These improvements position the sensors for next-generation applications, such as implantable devices and on-chip analytical platforms.

Finally, the proposed potentiometric method underwent a thorough greenness evaluation using multiple assessment tools, including GAM, Eco-Scale, GAPI, AGREE and the RGB12 model. The results confirmed compliance with the principles of both GAC (Green Analytical Chemistry) and WAC (White Analytical Chemistry). The developed method provides an eco-efficient, robust and sustainable solution for the selective determination of CPA in pure and combined dosage forms, representing a meaningful step forward in environmentally sensible pharmaceutical analysis.

References

[1] L. Yin, L. Yu, Y. Guo, C. Wang, Y. Ge, X. Zheng, N. Zhang, J. You, Y. Zhang and M. Shi, *J. Pharm. Anal*., 14, 101013 (2024).

[2] P. M. Nowak, *Green Chem*., 25, 4625-4640 (2023).

[3] E. Lindner and R. P. Buck, *Anal. Chem.*, 72, 336A–345A (2000).

[4] J. Hu, A. Stein and P. Bühlmann, *TrAC, Trends Anal. Chem.*, 76, 102–114 (2016).

[5] M.-R. Huang and X.-G. Li, *Prog. Mater Sci.*, 125, 100885 (2022).

[6] A. Lewenstam, in Comprehensive Analytical Chemistry, S. Alegret and A. Merkoçi, Eds., Elsevier, pp. 5–24 (2007).

[7] V. K. Gupta, M. R. Ganjali, P. Norouzi, H. Khani, A. Nayak and S. Agarwal, *Crit. Rev. Anal. Chem.*, 41, 282–313 (2011).

[8] R. De Marco, G. Clarke and B. Pejcic, *Electroanalysis*, 19, 1987–2001 (2007).

[9] B. Bansod, T. Kumar, R. Thakur, S. Rana and I. Singh, *Biosens. Bioelectron.*, 94, 443–455 (2017).

[10] G. Lisak, *Environ. Pollut.*, 289, 117882 (2021).

[11] A. Elsonbaty, A. M. Abdel-Raoof, S. Abdulwahab, W. S. Hassan and M. S. Eissa, *J. Electrochem. Soc.*, 168, 037518 (2021).

[12] A. S. Fayed, N. S. Ayish, B. A. El-Zeany and H. M. Marzouk, *Microchem. J.*, 165, 106127 (2021).

[13] M. A. Shehata, E. M. Fawaz, M. K. A. El-Rahman and E. M. Abdel-Moety, *J. Pharm. Biomed. Anal.*, 146, 179–187 (2017).

[14] M. M. Elhassan, A. M. Mahmoud, M. A. Hegazy and S. Mowaka, *Chem. Pap.*, 75, 4165–4176 (2021).

[15] E. Lindner and B. D. Pendley, *Anal. Chim. Acta*, 762, 1–13 (2013).

[16] M. P. S. Mousavi, M. K. Abd El-Rahman, E. K. W. Tan, H. H. Sigurslid, N. Arkan, J. S. Lane, G. M. Whitesides and P. Bühlmann, *Sens. Actuators B: Chem.*, 301, 127112 (2019).

[17] P. Bühlmann and L. D. Chen, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, P. A. Gale and J. W. Steed, Eds., John Wiley & Sons, Ltd., 2539–2579 (2012).

[18] S. A. Hassan, N. W. Nashat, M. R. Elghobashy, S. S. Abbas, A. A. Moustafa and A. M. Mahmoud, *Microchem. J.*, 178, 107323 (2022).

[19] M. Guzinski, J. M. Jarvis, B. D. Pendley and E. Lindner, *Anal. Chem.*, 87, 6654–6659 (2015).

[20] W. Kang, C. Rusinek, A. Bange, E. Haynes, W. R. Heineman and I. Papautsky, *Electroanalysis*, 29, 686–695 (2017).

[21] B. Thakur, E. Bernalte, J. P. Smith, C. W. Foster, P. E. Linton, S. N. Sawant and C. E. Banks, *Analyst*, 141, 1233–1238 (2016).

[22] S. Norita, D. Kumaki, Y. Kobayashi, T. Sato, K. Fukuda and S. Tokito, *Org. Electron.*, 25, 131–134 (2015).

[23] X. Pei, W. Kang, W. Yue, A. Bange, W. R. Heineman and I. Papautsky, *Anal. Chem.*, 86, 4893–4900 (2014).

[24] W. Kang, X. Pei, A. Bange, E. N. Haynes, W. R. Heineman and I. Papautsky, *Anal. Chem.*, 86, 12070–12077 (2014).

[25] M. R. Elghobashy, A. M. Mahmoud, M. R. Rezk, M. K. Abd El-Rahman, *J. Electrochem. Soc.*, 162, H1–H5 (2015).

[26] J.-P. Veder, R. De Marco, G. Clarke, R. Chester, A. Nelson, K. Prince, E. Pretsch and E. Bakker, *Anal. Chem.*, 80, 6731–6740 (2008).

[27] Ł. Górski, A. Matusevich, M. Pietrzak, L. Wang, M. E. Meyerhoff and E. Malinowska, *J. Solid State Electrochem.*, 13, 157–164 (2009).

[28] A. M. Mahmoud, M. N. Saad, E. S. Elzanfaly, S. M. Amer and H. M. Essam, *Anal. Methods*, 12, 2903–2913 (2020).

[29] J. Ping, Y. Wang, Y. Ying and J. Wu, *Anal. Chem.*, 84, 3473–3479 (2012).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2848-2859 | ISSN:2251-6727

[30] M. Y. Fares, N. S. Abdelwahab, M. A. Hegazy, M. M. Abdelrahman, A. M. Mahmoud and G. M. El-Sayed, *Anal. Chim. Acta*, 1192, 339350 (2022).
[31] S. Iijima, *Nature*, 354, 56–58 (1991).
[32] Y.-R. Wang, P. Hu, Q.-L. Liang, G.-A. Luo and Y.-M. Wang, *Chinese J. Anal. Chem.*, 36, 1011–1016 (2008).
[33] Y. Shao, Y. Ying and J. Ping, *Chem. Soc. Rev.*, 49, 4405–4465 (2020).
[34] G. A. Crespo, S. Macho, J. Bobacka and F. X. Rius, *Anal. Chem.*, 81, 676–681 (2009).
[35] M. Cuartero, J. Bishop, R. Walker, R. G. Acres, E. Bakker and R. De Marco, *Chem. Commun.*, 52, 9703–9706 (2016).
[36] United States Pharmacopeia and National Formulary (USP 39-NF 34) (2016).
[37] V. P. Hernandez-Trujillo and P. Lieberman, in Allergic Diseases: Diagnosis and Treatment, P. Lieberman and J. A. Anderson, Eds., Humana Press, Totowa, NJ, 319–334 (2007).
[38] B. L. Travi, *Med. Drug Discov.*, 15, 100140 (2022).
[39] W. Xu, S. Xia, J. Pu, Q. Wang, P. Li, L. Lu and S. Jiang, *Front. Microbiol.*, 9, 2643 (2018).
[40] D. Raynie and J. Driver, 13th Annual Green Chemistry and Engineering Conference, Maryland, USA (2009).
[41] A. Gałuszka, Z. M. Migaszewski, P. Konieczka and J. Namieśnik, *TrAC, Trends Anal. Chem.*, 37, 61–72 (2012).
[42] J. Płotka-Wasylka, *Talanta*, 181, 204–209 (2018).
[43] F. Pena-Pereira, W. Wojnowski and M. Tobiszewski, *Anal. Chem.*, 92, 10076–10082 (2020).
[44] P.M. Nowak, R. Wietecha-Posłuszny and J. Pawliszyn, *TrAC, Trends Anal. Chem.*, 138, 116223 (2021).
[45] Y. Liu, Y. Liu, Y. Gao and P. Wang, *Sens. Actuators B: Chem.*, 281, 705–712 (2019).
[46] R. P. Buck and E. Lindner, *Pure Appl. Chem.*, 66, 2527–2536 (1994).