



A Novel Potentiometric Sensor for Eletriptan hydrobromide based on 2, 6-di-O-methyl- β -Cyclodextrin-carbon nanotube platform: High Sensitivity and Wide Dynamic Range



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Abstract

The present study introduces an integrated screen-printed planner sensor for sensitive potentiometric determination of eletriptan hydrobromide (ELE). Comprehensive and deep optimization trials were performed concerning the impact of the sensing element, anionic sites, membrane plasticizer, carbonaceous nanostructures, electrode performance under different pH values, and other electroanalytical parameters. Among the different fabricated sensors, the printed sensor integrated with the 2,6-di-o-methyl β -cyclodextrin-multiwall carbon nanotubes platform (β -CD/MWCNTs) exhibit an ideal Nernstian slope value (59.7 ± 0.6 mV decade⁻¹) covering the ELE concentration ranged from 10^{-8} to 10^{-3} mol L⁻¹. The presented sensors offered highly stable potential reading, long operational lifetime, and fast dynamic response time (4s). The proposed sensors can be considered as a simple electroanalytical approach for fast and sensitive determination of ELE contents in authentic and commercial pharmaceutical products with average recovery value $100.11 \pm 1.3\%$.

Keywords: *Eletriptan hydrobromide; β -Cyclodextrin; Carbonaceous nanostructures; Potentiometric sensor; Pharmaceutical samples*

1. Introduction

As a new member of triptans, eletriptan hydrobromide (ELE) is commonly administrated for effcient medicinal treatment of migraine with/without aura [1]. As a selective 5-hydroxytryptamine (5-HT₁) receptor agonist, ELE selectively binds to vascular receptors which reduce the swelling of the blood vessels surrounding the brain to minimize the pain and headaches [2]. Two main theories explained the effectiveness of ELE agonists in treating migraines. The first postulated that vasoconstriction process is mainly caused through activation of the 5-HT₁ receptors found on the intracranial blood arteries. Alternatively, proinflammatory neuropeptide production was inhibited when 5-HT₁ receptors at sensory nerve terminals are activated [3, 4].

Among the few reported analytical approaches for monitoring ELE [5, 6], chromatographic and spectrometric methods are the most common. The reported chromatographic separation techniques included RP-HPLC [7-9], and LC-MS methods [10]. In addition, fluorometric and spectrophotometric methods were also applied [11-14]. With a reported sensitivity and selectivity towards ELE determination, the chromatographic and spectrometric methods showed several drawbacks as they operate with tedious and sophisticated analytical protocol with several derivatization steps, require expensive equipments, and handling of hazard organic solvents. These drawbacks hinder the recommendation of the spectroscopic or chromatographic methods for continuous monitoring of the pharmaceutical residues in environmental samples. As an efficient medicinal that commonly administrated for migraine treatment, the development of a novel simple and sensitive analytical approach for monitoring of ELE is required.

Electroanalytical approaches accompanied with integrated electrochemical sensors showed the advantages of sensitive and fast analysis with simple measurement equipment compared with the chromatographic separation techniques [15]. Among electrochemical sensors, potentiometric sensors (mainly ion selective electrodes) can be considered as the most simple and common electroanalytical tool for detection of pharmaceutically active compounds in their pharmaceutical formulations [16-24].

Molecular recognition elements offer a promising alternative sensing mechanism for construction of integrated potentiometric sensors through selective formation of host-guest inclusion complex accompanied with noticeable enhancement of selectivity and sensitivity of the potentiometric sensor compared with the ion-associate (ion-pair formation) sensing mechanism [25-28]. The common host-guest interactions forces are based π - π interaction, van der Waals forces, dipole-dipole interaction, and hydrogen bonding forces. Macrocyclic cyclodextrins (CDs) were reported as the popular sensing elements for potentiometric and voltammetric sensors. The lipophobic interior cavity of the CDs moiety offers an ideal environment for fitting the lipophobic part of the guest molecule. Generally, the stability constant of the resulted inclusion complex is governed mainly

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by applied CDs cavity size which is compatible with the guest size in addition to the side derivatization on the CDs ring. Careful survey of the reported literatures revealed a sole ELE-PVC membrane potentiometric sensor enriched with α - or β -CDs as sensing element in the presence of potassium tetrakis (4-chlorophenyl)borate (KTCIPB) as anionic sites and dioctyl phthalate (DOP) as membrane plasticizer [29]. The cited sensors recorded near Nernstian response within the ELE concentration ranged from 1.0×10^{-6} to 1.0×10^{-2} molL⁻¹ and detection limit 4×10^{-6} molL⁻¹. Relatively slow response time (20s) and short operational lifetime were the obviously reported disadvantages of the reported sensor. Moreover, the PVC membrane based sensors are mechanically complicated, too bulky, and required sterilization for biomedical applications, with relatively short operational lifetimes. With a contentious rising in the consumption of mendicants, commercial disposable electrochemical sensors were adopted as a part of commercial portable devices for screening of pharmaceutically active compounds. Application of screen-printing technology offers the large scale production of highly reproducible low cost planner disposable electrochemical sensors [30-34].

Carbonaceous nanomaterial integrated sensors represent the major category of the tailor-made electrochemical sensors with enhanced performance by leveraging the electrocatalytic activity of nanoparticles, accelerating of the electron transfer process, and converting of the chemical interaction to electrical signal [35-37].

In our previous work [38], multiwall carbon nanotubes (MWCNTs) functionalized carbon paste electrodes were applied for differential pulse voltammetric determination of ELE within the concentration range from 0.027 to 1.1 $\mu\text{g mL}^{-1}$ and limit of detection 8 ng mL⁻¹. Herein, novel screen-printed planner disposable electrochemical sensors were fabricated for sensitive and simple potentiometric analysis of eletriptan in the marketed pharmaceutical tablets applying different cyclodextrins derivatives as sensing element and single wall carbon nanotubes as transducers. Research plain was followed concerning the nature of the membrane components including sensing element, ionic sites, plasticizer, and carbonaceous nanostructure, the effect of pH, and other electroanalytical parameters were also specified. The fabricated sensors were validated following the ICH guidelines for monitoring ELE.

2. Experimental

2.1. Eletriptan authentic sample and applied chemicals

The applied chemicals and reagents were of analytical grade and ultrapure water was used. The eletriptan hydrobromide authentic standard sample ((R)-3-[(1-methyl-2- pyrrolidinyl)methyl]- 5-[2-(phenylsulfonyl)ethyl]-1H-indole mono hydrobromide, C₂₂H₂₇BrN₂O₂S, M.wt. 463.4 g mol⁻¹, purity of the authentic sample was assigned to be 99.25%) was obtained from the Standard Laboratory, Egyptian Drug Authority (EDA). The stock ELE solution was prepared by dissolving an appropriate amount of the certified ELE sample in 25.0 mL water and kept at 4°C for two weeks.

The applied cyclodextrin derivatives (Sigma-Aldrich) were α -CD (**I**), γ -CD (**II**), β -CD (**III**), in addition to the methylated β -CD derivatives 2,6-di-O-methyl- β -CD (**IV**), and 2,3,6-tri-O-methyl- β -CD (**V**). Different tetraphenylborate derivatives were applied as ionic sites including: sodium tetraphenylborate (NaTPB, Fluka), sodium tetrakis (4-fluorophenyl) borate (NaTFPB, Fluka) or potassium tetrakis (4-chlorophenyl) borate (KTCIPB, Fluka). Dioctylphthalate (DOP, Sigma), dioctylsebacate (DOS, Avocado), tricresylphosphate (TCP, Fluka), 2-fluorophenyl-2-nitrophenyl ether (*f*-PNPE, Fluka), or *o*-nitro-phenyloctylether (*o*-NPOE, Sigma) were applied as membrane plasticizers.

High molecular weight polyvinyl chloride (PVC) and graphite powder (Gr, Aldrich) were utilized in manufacturing of the sensing membrane matrix and the printing carbon ink. Different carbonaceous nanostructures were applied as electrode modifier including multiwall carbon nanotubes (MWCNTs, Aldrich), singlewalled carbon nanotubes (SWCNTs, Aldrich), and reduced graphene (rG, Sigma).

2.2. Measuring system and electrodes

A PC-based EMF-16 high-resolution data logger (LAWSON, USA) was used to record and manipulate the potentiometric output signals. The six channel instrument allows the parallel recording of the potential readings for six different sensors at the same time under the same measuring conditions for more accuracy and precision. pH measurements were performed using a 692-pH meter with a combined glass electrode (Metrohm, Switzerland).

The planner screen printed sensors were printed on the overhead projector PET sheet as discussed in details elsewhere [39, 40]. The sensing membrane was prepared by dissolving 2.0 mg of 2,6-di-O-methyl- β -CD (**IV**), and 1.0 mg NaTFPB in 360 mg *f*-PNPE with contentious stirring for 15 min. Added 6 mL of THF, 240 mg PVC, and 15.0 mg MWCNTs were added to the above matrix under stirring followed by sonication for 2 h. 20 μL of the homogeneous sensing cocktail were dropcasted on the graphite/PVC conducting track and left to dry for 24 h at 25 °C. Before using, the fresh sensors were soaked in 10^{-4} molL⁻¹ ELE solution for 15 min till the steady state potential reading.

2.3. Measuring procedures

The printed potentiometric sensors were immersed in the measuring cell containing 5mL of ELE solution with ascending concentrations from 10^{-9} to 10^{-3} molL⁻¹ at 25°C. The potential readings were recorded and plotted against the ELE concentrations in logarithmic scale [41].

2.4. Sample analysis

The commercial ELE samples (Replax, 40 mg ELE/tablet, Pfizer, Egypt) were purchased from local stores. The stock ELE pharmaceutical solution was prepared by dissolving the crushed tablet in water followed by ultrasonication for 15 min at 50°C. Further dilution to a suitable ELE concentration was carried out and the ELE content was assayed at the optimized potentiometric conditions compared with the spectrophotometric method [12]. Defined increments of the stock ELE solution

were mixed with the pharmaceutical sample solution. After each addition, the potentials readings were recorded and the ELE concentration in the pharmaceutical sample solution was calculated [42].

3. Results and discussion

Cyclodextrins (CDs) are macrocyclic oligosaccharides formed from 1,4-glucosidic bond linked (β) glucopyranose oligomers of 6, 7, and 8 glucose units yielding α -, β -, and γ -CDs, respectively [28, 43]. The hydroxyl groups of glucopyranose subunits are orientated to the exterior of CD molecule, whereas the central cavity, lined with skeletal carbon and ether oxygen atoms of the glucopyranose units; therefore the CD exterior is hydrophilic while the interior is relatively hydrophobic. The hydrophobic CD cavity can fit the appropriately sized nonpolar guest molecule, or more often nonpolar parts forming an inclusion complex [44]. The stability and binding forces of the host-guest inclusion complexes are attributed to number of factors, such as cavity size, shape and configuration of the guest molecule and the derivatization at the ring sides. As reported elsewhere [29], ELE forms 1:1 host-guest complexes with β -CD revealed the binding affinity and one H-bond interaction within the complex. The sulfonyl group of eletriptan molecule interacted with the OH group of β -CD at a distance of 2.26 Å.

3.1. Optimization of the electrode matrix composition

3.1.1. Nature of the sensing element

The sensing mechanism of the presented sensors based on the molecular interaction between the ELE and CDs molecules where the potentiometric response is governed by the affinity of the CDs towards the ELE molecule and the stability constant of the corresponding inclusion complexes. Bare electrodes formulated in the absence of the sensing element showed non-Nernstian slope value (46.2 ± 3.2 mVdecade⁻¹), while sensors enriched with different cyclodextrin derivatives (**I** to **V**) exhibited Nernstian responses depending on the applied ionophore (**Figure 1**). α -, β -, and γ -cyclodextrin processes the same ring height but differ only in their corresponding ring size. Cyclodextrin responded differently towards ELE molecule based on their cavity size appropriate for fitting ELE molecule. α -CD (**I**) showed lower Nernstian response (50.9 ± 0.5 mVdecade⁻¹) covering the ELE concentration ranged from 10^{-6} to 10^{-2} mol L⁻¹, based on their inappropriate cavity size for complexation with ELE molecule. With a relatively higher Nernstian compliance (54.4 ± 1.6 mVdecade⁻¹), γ -CD (**II**) responded to ELE with more suitable cavity size. On the other hand, sensors integrated with either β -cyclodextrin or its methylated derivatives showed proper responses (53.4 ± 2.4 , 58.5 ± 0.9 , and 56.2 ± 2.7 mVdecade⁻¹ for ionophores **III**, **IV** and **V**, respectively) with a wide linear concentration ranged from 10^{-8} to 10^{-2} mol L⁻¹ related to their ring cavity size and the more stable inclusion complexes.

The native cyclodextrins have ring height of 8°A, therefore part of ELE molecule may remain outside the cage (vide infra). Side derivatization with methyl groups (compounds **IV**, **V**) enlarge the ring cavity to 11 °A [45], enhance of the hydrophobicity of the ring side, and offer extra locations for substrate binding [46, 47]. These factors may enhance the penetration of ELE molecule inside the CD cavity, which in turn the stabilized of the formed inclusion complex compared to native β -CD. However, some effects of steric hindrance due to the presence of three methyl groups (**V**) may present which reduce the Nernstian response.

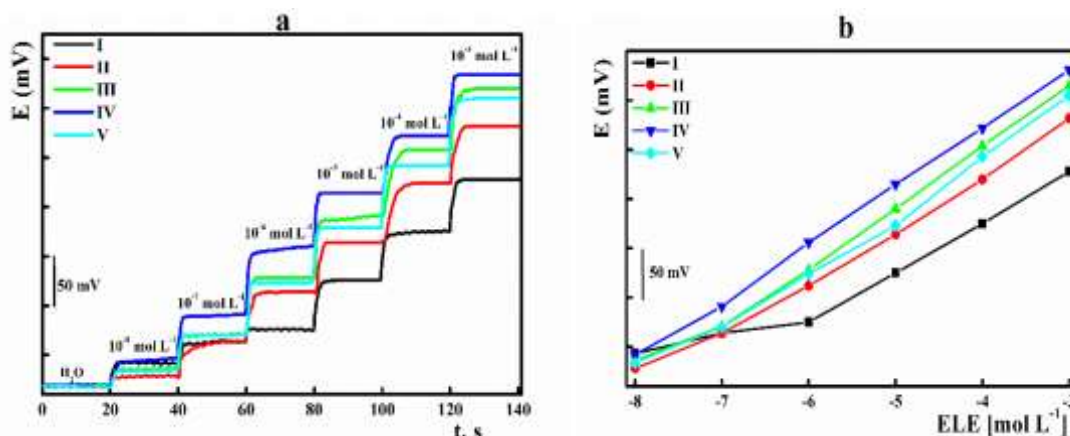


Figure 1: a) Potentiometric behaviour of the ELE SPEs incorporated with different cyclodextrin derivatives, and b) linear calibration graphs of ELE SPEs incorporated with different cyclodextrin derivatives.

3.1.2. A Anionic sites effect

As a neutral carrier ionophore, β -CDs based potentiometric sensors operate only in the presence of charged sites [48-50]. Addition of such ionic sites, with opposite charge to ELE molecule, attracts ELE from the bulk solution to the sensing membrane/solution interface to form β -CDs-ELE inclusion complex, reduces the membrane resistance, and accelerate the ion-exchange kinetics at the membrane interface which resulted in improvement of the sensor performance. Therefore, the performances of the ELE sensors modified with different tetraphenylborate derivatives were tested in the presence of 2,6-di-O-methyl β -cyclodextrin (**IV**) as a selected recognition element (**Figure 2**).

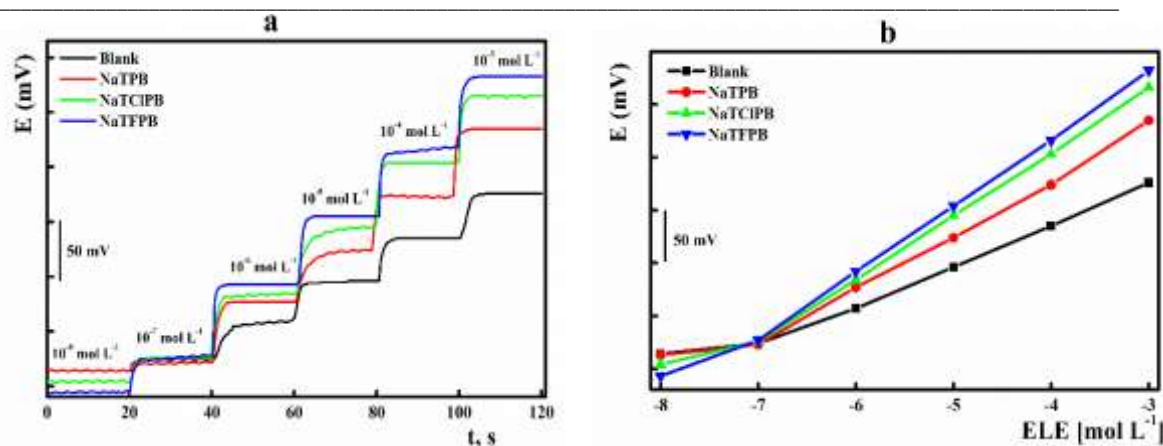


Figure 2: a) Potentiometric behaviour of the ELE SPEs incorporated with 2,6-di-O-methyl β -cyclodextrin (IV) in the presence of different anionic sites, and b) linear calibration graphs of ELE SPEs applying different tetraphenylborate derivatives.

As illustrated in Figure 2b, the sensor performance was improved in the presence of different tetraphenyl borate derivatives compared to the blank electrode. Among the tested anionic sites, NaTFPB showed the highest Nernstian slope value (38.2 ± 0.8 , 52.1 ± 1.4 , 59.9 ± 0.5 , and 63.4 ± 0.5 mVdecade⁻¹ for the bare, NaTPB, KTCIPB, and NaTFPB respectively). Substitution in the para position with more electronegative atom enhances the electron withdrawing force which increases the negative charge on the boron atom which in turn increases the efficiency of the electrode.

3.1.3. Impact of the membrane plasticizer

The potentiometric performance of the ionophore-based sensors is mainly governed by the polarity of the sensing membrane, defined by the dielectric constant value (ϵ) of the membrane plasticizer. Moreover, membrane plasticizer controlled the mobility of the recognition element and the formed β -CDs-ELE inclusion complexes [50, 51]. In the present study (Figure 3), five membrane plasticizers with different dielectric constant values were applied namely; *f*-PNPE, *o*-NPOE, TCP, DOP, and DOS ($\epsilon=50$, 24.8, 17.6, 3.8, and 5.2, respectively) [52].

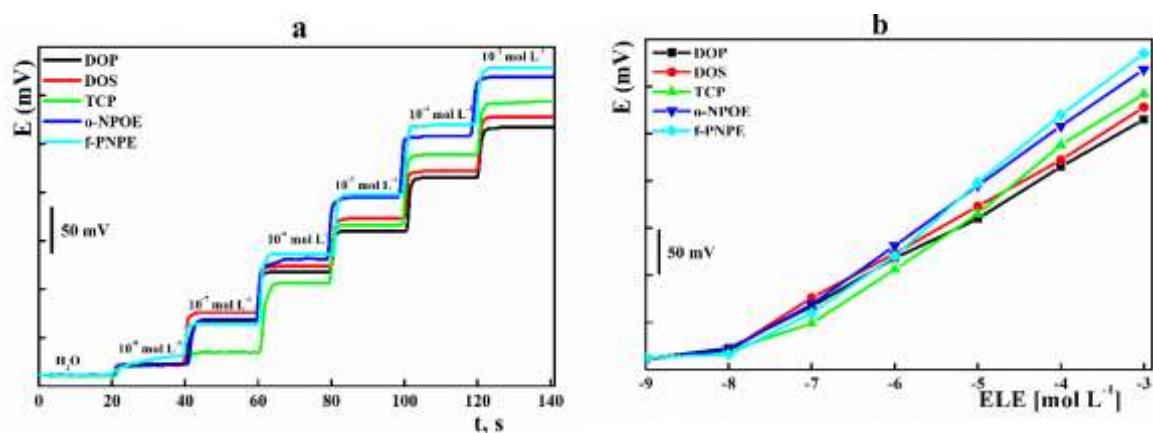


Figure 3: a) Potentiometric behaviour of the ELE SPEs incorporated with 2,6-di-O-methyl β -cyclodextrin (IV) and NaTFPB in the presence of different membrane plasticizers, and b) linear calibration graphs of ELE SPEs in the presence of different membrane plasticizers.

Noticeable improvement in the electrode performance was recorded (Figure 3b) applying high polar plasticizers with ideal Nernstian slope values compared with those having lower dielectric constants (61.5 ± 1.8 , 60.5 ± 1.4 , 48.8 ± 0.8 , 50.8 ± 0.7 , and 54.6 ± 1.4 mVdecade⁻¹ for *f*-PNPE, *o*-NPOE, DOP, DOS, and TCP, respectively).

3.1.4. Nanomaterial impact

Based on their unique promising futures, integration of the electrode matrix nanomaterials enhances the transduction of the possible chemical interaction to a measurable electrical signal and electroactive surface area [53-58]. Herein, the sensing matrix at the optimum composition containing 2,6-di-O-methyl β -cyclodextrin (IV) as sensing element, NaTFPB as anionic sites and *f*-PNPE as membrane plasticizer were integrated with different carbonaceous nanomaterials including synthetic graphite (Gr), reduced graphene oxide (rG), MWCNTs or SWCNTs. As presented in Figure 4a, b, modification of the electrode matrix with MWCNTs enhanced the sensor's performance with the highest Nernstian slope value 59.7 ± 0.6 mVdecade⁻¹ covering the ELE concentration range from 1.0×10^{-8} to 1.0×10^{-3} mol L⁻¹ (Figure 4 a, b).

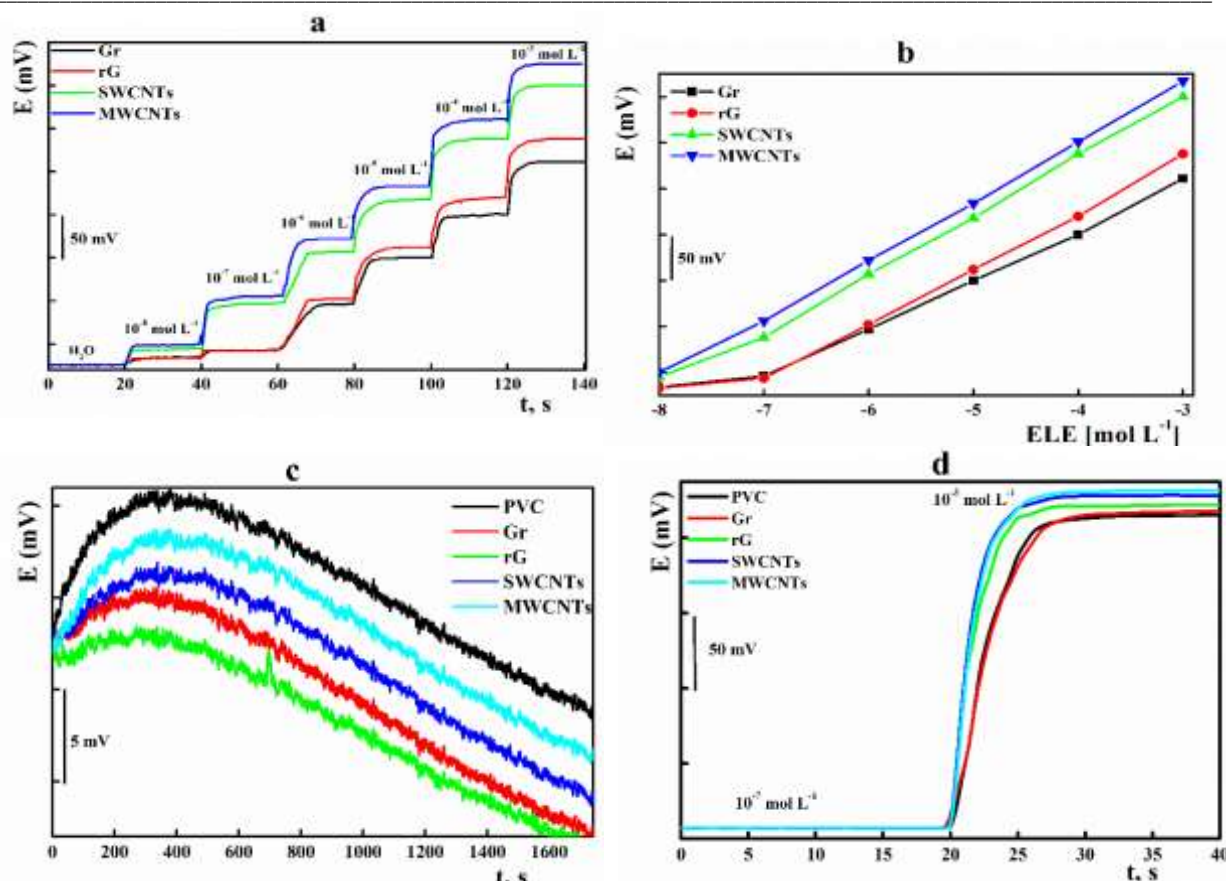


Figure 4: Impact of the carbonaceous nanomaterial on; a, b) potentiometric behaviour of ELE sensors; c) potential stability; d) ELE-SPEs response time.

Based on the solid state nature of the fabricated sensors and the absence of the internal filling solution, the ELE sensor showed stable potential readings indicated by the short preconditioning time (the time required to attain steady state potential reading for the fresh used electrode) which is a critical requirement of the disposable sensors. Enrichment of the sensing matrix cocktail with the aforementioned nanomaterials increases the hydrophobicity of the sensing membrane/measuring solution interface which enhances the potential stability. Intergradation with MWCNTs attained more stable potential readings within 15 min soaking compared with other tested nanostructures and bare electrodes (**Figure 4c**).

For reasonable electroanalytical applications of potentiometric sensors and monitoring kinetic reactions, the dynamic electrode response time (the required time to achieve 90% of the total potential jump after sudden tenfold increase in the ELE concentration) is crucial. Therefore, the impact of different nanostructures on the ELE sensor response time was recorded by sudden change in the ELE concentration 1×10^{-7} to 1×10^{-3} mol L $^{-1}$ (**Figure 4d**). Fast response times (ranged from 3 to 5 s) were achieved where MWCNTs based sensors were the best.

3.2. Validation of the sensor

The performance characteristics of introduced ELE SPEs integrated with β -CD (**IV**)-MWCNTs composite was evaluated following IUPAC recommendation and compared with the ELE PVC sensors (**Table 1**). The novel ELE-SPEs showed enhanced performance regarding the wide dynamic linear range, lower detection limit, faster response time, and the prolonged operational lifetime of the disposable sensors with the possibility of commercialization and miniaturization avoiding the mechanically complicated and bulky PVC membrane electrodes.

One of the most promising futures of the fabrication of the ELE sensors by screen printing technology is the high reproducible and large-scale production of planner electrochemical sensors. The fabrication reproducibility was evaluated by calibration of ten printed sensors from the same batch, where the average Nernstian slope value was 58.8 ± 1.1 mV/decade $^{-1}$. The printed sensors can be categorized belong to the solid contact sensors; therefore prolonged lifetime about 24 weeks was reported. Even though, the fabricated sensors are disposable, the same sensors can operate contentiously up to 4 weeks with acceptable performance.

Table 1: Electroanalytical parameters of the ELE potentiometric sensors

Parameter	Present	Ref. 29
Sensing element	2, 6-di-O-methyl β -CD (IV)-MWCNTs	α -, β -CD
Electrode configuration	Screen printed	PVC
Linear range (molL ⁻¹)	10 ⁻⁸ -10 ⁻³	7.0 \times 10 ⁻⁶ -10 ⁻²
Slope (mV decade ⁻¹)	59.7 \pm 0.6	58.9 \pm 0.5
R	0.9990	0.9970
LOD (molL ⁻¹)	1.0 \times 10 ⁻⁸	4.0 \times 10 ⁻⁶
Response time (s)	3.0	20 \pm 0.5
Preconditioning time	15 min	24 h
Working pH range	3.0-9.0	4.0-8.5
Shelf-life time (week)	24	5

For a successful application of a newly developed potentiometric sensors, the working pH range is usually questionable. In the present study, the impact of the pH on the electrode response was monitored within a wide pH range from 2 to 12. The pH value was controlled by addition of small aliquots of concentrated HCl or NaOH solutions to the measuring cell (**Figure 5**). The fabricated sensors showed stable potential within the pH value ranged from 3 to 8. At higher pH values, the ELE potential decreased dramatically due to the formation of unprotonated ELE species (pKa value for ELE molecule is 8.05), while at lower pH values, the ELE sensors potential are severely influenced by H₃O⁺ species.

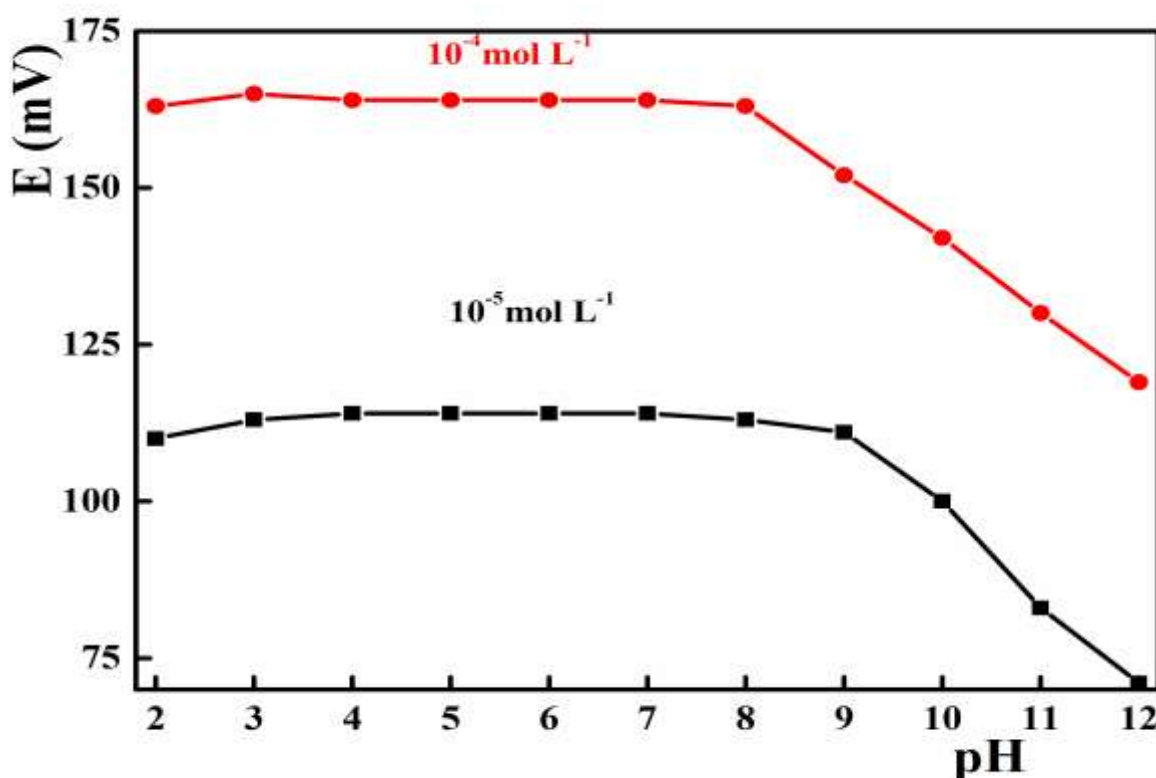


Figure 5: Performance of the fabricated ELE sensors at different pH values

3.3. Selectivity studies

The selectivity of newly introduced analytical approach against the target analyte in the presence of additives and excipients in the marketed pharmaceutical product represents a crucial issue. The selectivity of the potentiometric sensors nominated to their ability to differentiate the target analyte from the interfering species and expressed by selectivity coefficient [59]. Matched potential method (MPM) is the most common method for measuring the selectivity coefficient of the potentiometric sensors and can operate in the presence of neutral compounds or different charged analytes [60]. The selectivity of the ELS-SPEs based on 2, 6-di-O-methyl β -CD (IV)-MWCNTs against ELE was promoted via formation of ELE- β -CD inclusion complex (**Table 2**).

Table 2: Selectivity coefficients of the ELE-SPEs based on 2, 6-di-O-methyl β -CD (IV)-MWCNTs

Interferent	$-\log K_{A,B}^*$	Interferent	$-\log K_{A,B}$
Li ⁺	3.60	Croscarmellose	4.20
NH ₄ ⁺	3.10	Sucrose	4.05
Ca ²⁺	2.98	Glucose	4.40
Magnesium stearate	3.25	Fructose	3.60
Titanium dioxide	3.44	Glycine	3.29
Co ²⁺	3.90	Caffeine	3.35
Phosphate	3.53	Cysteine	2.85
Citrate	3.70	Sunset Yellow FCF	3.40
Lactose	3.90	Aluminium Lake (E110)	2.80
Starch	3.74	Glycerol triacetate	3.19

* Lower and upper concentrations of ELE, 10^{-6} and 10^{-3} molL⁻¹, respectively.

3.4. Analysis of ELE samples

Based on the recorded satisfactory and improved sensitivity and selectivity of the presented ELE sensor, the modified sensors enriched with β -CD-MWCNTs can be suggested as an efficient analytical tool for monitoring of ELE in the authentic solution and pharmaceutical formulations. Data presented in **Table 3** showed satisfactory agreement for the ELE content in analysed samples based on the proposed electroanalytical approach and the official methods.

Table 3: Potentiometric determination of ELE in the authentic solution and commercial and pharmaceutical sample

Sample	Taken (μ g)	Replax, 40 mg/tablet					
		Authentic					
		Found (μ g)	Recovery	RSD	Found (μ g)	Recovery	RSD
Standard addition	3.82	3.640	95.32	2.8	3.557	93.13	3.6
	38.2	37.640	98.54	1.9	35.168	96.22	2.4
	382	382.420	100.11	1.3	374.78	98.10	2.1

* Mean recovery and relative standard deviations of three determinations

4. Conclusion

The present study introduces the construction and electroanalytical validation of novel eletriptan hydrobromide planner disposable potentiometric sensors modified with 2, 6-di-O-methyl β -cyclodextrin (IV)-MWCNTs composite as molecular recognition element. The fabricated sensors showed an ideal Nernstian response of 59.7 ± 0.6 mV decade⁻¹ within the dynamic linear concentration ranged from 10^{-8} to 10^{-3} molL⁻¹ with fast response time about 3 s and long lifetime about 24 weeks. Based on the reported sensitivity and selectivity, the introduced sensors can be applied for routine analysis of ELE in various samples with acceptable average recovery values. Improved electroanalytical characteristics were reported compared with the ELE-PVC sensors regarding their sensitivity, response time, and operational life time.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

No Funding source.

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