Voltammetric determination of phenylephrine hydrochloride using a multi-walled carbon nanotube-modified carbon paste electrode

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A chemically modified carbon paste electrode (CPE) was designed by mixing graphite and multi-walled carbon nanotubes (MWCNT). The electrochemical behaviour was studied, and the determination method of phenylephrine hydrochloride (PHE) on this sensor was established. According to the results, the optimal ratio of MWCNTs was approximately 12.5% (w/w). MWCNT-modified carbon paste electrodes (MWCNT-CPEs) showed high electrochemical activity for PHE, producing a sharp oxidation peak current (I_p) at approximately +0.816 V versus a saturated calomel electrode (SCE) reference electrode in phosphate buffer solution (PBS, pH 6.45), and the I_p increased by approximately two times compared to that of the bare CPE. The anodic I_p was linearly related with 5.0 × 10⁻⁶–7.5 × 10⁻⁴ mol l⁻¹ PHE, with a detection limit of 3.7 × 10⁻⁷ mol l⁻¹. Furthermore, MWCNT-CPEs were successfully applied to the determination of PHE in injection, eye drop and nasal spray liquid samples as a simple, rapid and low-cost method.

1. Introduction

Phenylephrine hydrochloride (PHE) (scheme 1) is an adrenergic receptor agonist that acts on α receptors in skin, mucosa, viscera and other tissues, to contract blood vessel and increase blood pressure. Clinically, it is mainly used to maintain a stable blood pressure during shock and under anaesthesia, and it can also be
used to eliminate inflammation of nasal mucosa, dilate the pupils, etc. Pharmaceutical dosage forms are mainly injection, eye drops and nasal spray liquid and concentrations are within 0.1–1% (w/v).

At present, determination methods of PHE include HPLC [1,2], UPLC-MS [3], spectrophotometry [4,5] and capillary electrophoresis [6,7]. The pretreatment processes of these methods are relatively complex, requiring large-scale instruments. Thus, they are not convenient for on-site quick detection. The sample pretreatment process of electrochemical determination is relatively simple, i.e. it is a convenient and fast measuring process using inexpensive instruments. Meanwhile, a chemically modified carbon paste electrode (CM-CPE) can improve selectivity and sensitivity of the CPE and integrate separation, enrichment and selective determination into a single step; therefore, it is one research focus of the analysis and detection field [8–10]. Our research group has made some achievements in the research of modified CPE [11–13].

It has also been reported that a modified glassy carbon electrode (GCE) can be used to detect PHE [14,15], while reports on using modified CPE to detect PHE are relatively rare [16,17]. Because of the high sensitivity and convenience in making and updating multi-walled carbon nanotube carbon paste electrodes (MWCNT-CPEs), this paper used MWCNT-CPEs as the working electrode, researched the electrochemical behaviour of PHE on the electrode and established the method of direct determination of PHE. Furthermore, different dosage forms were detected, such as injection, eye drops and nasal spray liquid, with satisfactory results. The method does not require complex pretreatment of samples and combined with a small portable electrochemical workstation, samples can be detected on site, i.e. there is no need to send them to professional laboratories.

2. Experimental set-up

2.1. Apparatus and chemicals

Cyclic voltammetry (CV) was performed on an Ingsens-1010 series hand-held electrochemical workstation (Ingsens Instruments, Guangzhou, China). A conventional three-electrode system with an MWCNT-CPE (home-made) as the workstation, a saturated calomel electrode (SCE; Chenhua Instruments, Shanghai, China) as the reference electrode and a platinum electrode (Chenhua Instruments, Shanghai, China) as the indicating electrode was used. A pH meter (pHS-25, Leici Instrument, Shanghai, China) with a double junction glass electrode was used to check the pH of the solutions.

PHE (99%), MWCNTs (SP, 3–5 nm in diameter), graphite powder (SP, 40 nm) and liquid paraffin (HPLC) were purchased from Shanghai Aladdin Reagent Co., Ltd. Other chemicals were analytically pure, and the water used in the experiment was deionized water.

2.2. Preparation of solutions

A 1.0 × 10⁻³ mol l⁻¹ PHE solution was prepared by dissolving 20.37 mg of PHE standard substance in 100 ml of deionized water, and the solution was kept in a refrigerator at 4°C. Phosphate buffer solution (PBS) with different pH values was prepared by mixing stock solutions of NaH₂PO₄ and KH₂PO₄, and the pH was adjusted with H₃PO₄ and NaOH.

The product instruction manual showed that the main component of PHE injection is deoxidation PHE, and the auxiliary materials are sodium metabisulfite, sodium chloride and edetate disodium. The main components of compound tropicamide eye drops are tropicamide and PHE. The main components of compound PHE nasal spray liquid are PHE, dexamethasone sodium phosphate and lincomycin hydrochloride. The above samples did not need pretreatment. An appropriate amount of sample can be directly measured and was diluted with PBS (pH = 6.45) to the required concentration.

2.3. Preparation of MWCNT-CPE

MWCNT-CPE was made by mixing graphite powder, MWCNTs and liquid paraffin evenly with a certain ratio. The mixture was placed in a glass tube with a radius of 2.0 mm and compacted. Copper
wire was used as a guide line, and the electrode was fixed after drawing off the guide line. Then, the surface of the electrode was smoothed and polished on a piece of smooth white paper.

Based on the above methods, we also obtained bare CPE with no MWCNTs added.

2.4. Electrochemical analysis procedure

An appropriate amount of PHE solution was placed in a small beaker, and the three-electrode system was inserted. The enrichment time was adjusted to 10 s and the scan speed was 400 mV s\(^{-1}\). The initial and final potentials were from 0.2 to 1.0 V, and the peak voltage \(E_p\), peak current \(I_p\) and other information were recorded.

After the detection was completed, the working electrode was placed into a 0.1 mol l\(^{-1}\) NaOH solution and cyclically scanned 10 times to clear PHE adsorbed on the electrode.

3. Results and discussion

3.1. Characteristics of the MWCNT-CPE using cyclic voltammetry

The electrochemical behaviour of PHE was researched using MWCNT-CPE and CPE, i.e. two different kinds of electrodes, to, respectively, scan in blank or 5.0 \(\times\) \(10^{-5}\) mol l\(^{-1}\) PHE solution (figure 1). The anodic \(E_p\) is approximately 0.82 V, and no cathode peak is observed, which shows that PHE oxidation is irreversible on the electrode. The \(I_p\) of PHE on CPE (b) is relatively less; and the \(I_p\) is increased by approximately two times on MWCNT-CPE (a).

3.2. Effect of amount of MWCNTs

To obtain the optimal conditions to improve electrochemical performance, the ratio of MWCNTs added was studied. MWCNTs were mixed with graphite powder with a certain ratio, and an appropriate amount of liquid paraffin was added to obtain five MWCNT-CPEs. Scanning was conducted in 5.0 \(\times\) \(10^{-5}\) mol l\(^{-1}\) PHE solution (figure 2), and it shows that when the ratio of MWCNTs and graphite powder is 12.5\% (figure 2a), the \(I_p\) is relatively higher, and the peak shape is better.

3.3. Effect of buffer solution

Britton–Robinson (BR), KH\(_2\)PO\(_4\)-H\(_3\)PO\(_4\), Na\(_2\)HPO\(_4\)-citric acid, NaAc-HAc, NH\(_3\)-NH\(_4\)Cl, PBS and other buffer solutions were used to dilute PHE solutions to 5.0 \(\times\) \(10^{-5}\) mol l\(^{-1}\), and cyclic scanning was conducted on the above solutions. We found anodic peaks for BR, KH\(_2\)PO\(_4\)-H\(_3\)PO\(_4\), NH\(_3\)-NH\(_4\)Cl and PBS, while the peak shape in BR is not obvious and is unstable, and the \(E_p\) is approximately 0.60 V; \(E_p\)s in NH\(_3\)-NH\(_4\)Cl and PBS are approximately 0.82 V. The peak shape in PBS is better, and the \(I_p\) is higher. Furthermore, various experiments show that reproducibility in PBS is also better.
3.4. Effect of pH

The influence of pH on $I_p$ (5.0 $\times$ 10$^{-5}$ mol l$^{-1}$ PHE) by CV in PBS with various degrees of acidity was examined, and according to figure 3, the $I_p$ increases to its peak and then decreases (figure 3b). When the pH is 6.16 and 6.45, the $I_p$ is larger and the peak pattern is better (figure 3a); therefore, PBS at pH of 6.45 is chosen in the following experiment.

Furthermore, it is also found that PHE $E_p$ decreases with the increase in pH, and there is also a linear relationship between them (figure 3c), which indicates that protons are involved in the PHE oxidation.
reaction. When the pH is within 3.95–8.34, the linear equation between $E$ and pH is $E = 1.1468 - 0.0571 \text{pH}$ ($r = 0.9991$), and the slope is 0.057. According to the Nernst equation, the proportion of electrons to protons participating in the redox reaction is 1 : 1 based on the slope of 0.059. Thus, PHE on MWCNT-CPEs is a redox reaction with an electron-to-proton ratio of 1 : 1.

3.5. Effect of accumulation time

The influence of accumulation time on the $I_p$ for two different PHE concentrations was investigated, and when the concentration is 1.0 $\times 10^{-5}$ mol l$^{-1}$, the $I_p$ reaches the maximum in 10 s. When the concentration is 5.0 $\times 10^{-5}$ mol l$^{-1}$, with increasing accumulation time, there is no significant change in $I_p$; therefore, the accumulation time in the following experiment is 10 s.

3.6. Effect of scan rate

The effect of scan rate on the electrochemical behaviour of PHE was investigated at the MWCNT-CPE by CV. In PBS-buffered solution with pH 6.45, accumulation time of 10 s, and PHE concentration of 5.0 $\times 10^{-5}$ mol l$^{-1}$, the scan rate was changed from 50 to 800 mV S$^{-1}$, and the changes in $I_p$ and $E_p$ of PHE were recorded (figure 4a); with an increasing scan rate, the $I_p$ as well as $E_p$ gradually increases.

In the experiment, it is also found that there is a good linear relationship (figure 4b) between the $I_p$ and scan rate. The linear equation of $I$ and $v$ is $I = 0.0099v + 0.6147$ ($r = 0.9990$), which illustrates that the redox reaction of PHE on MWCNT-CPE is mainly adsorption controlled.

In addition, there is also a good linear relationship (figure 4c) between $E$ and the $\ln v$, and the linear equation is:

$$E = 0.0223\ln v + 0.6863 \quad (r = 0.995).$$

Figure 4. (a) Cyclic voltammograms of 5.0 $\times 10^{-5}$ mol l$^{-1}$ PHE in phosphate mixture at different scan rates of 50–800 mV s$^{-1}$. (b) Linear relationship of $I_p$ versus scan rate. (c) Linear relationship of $E_p$ versus $\ln v$. 

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According to reversible electrode reactions, the following relationship exists between the $E_p$ and scan rate [18]:

$$E_p = E^\circ - \frac{RT}{\alpha nF} \left[ 0.78 - \ln \frac{k^0}{D^{1/2}} + \ln \left( \frac{\alpha nFv}{RT} \right)^{1/2} \right],$$

where $\alpha$ is the charge transfer coefficient, $n$ is the number of transferred electrons, $R$ is the gas constant (8.314 J K$^{-1}$), $T$ is the temperature (K, 298) and $F$ is the Faraday constant (96487 C mol$^{-1}$).

Combining equation (3.1) with (3.2), $1/2 \times RT/\alpha nF = 0.0223$, and $\alpha n$ is calculated to be 0.58. The value of $\alpha$ is assumed to be 0.5 for an irreversible electrochemical process [19], and the electron participating in the reaction is calculated as 1.16 (close to 1). Combining the conclusions from before, the reaction mechanism of PHE on MWCT-CPE is shown in scheme 2.

3.7. Interference studies

Some common substances or constituents of pharmaceutical formulations were added to a 5 x 10$^{-5}$ mol l$^{-1}$ PHE solution, and the changes in $I_p$ and $E_p$ were measured (table 1). The result shows that these substances have no interference on PHE detection, and this sensor is highly selective for PHE.

| substances              | amount (mol l$^{-1}$) | $I_p$ (µA) | relative error (%) | $E_p$ (V) | relative error (%) |
|-------------------------|-----------------------|------------|-------------------|-----------|-------------------|
| none                    | 10.99                 | 10.99      | 0.816             |
| NaCl                    | 0.05                  | 11.11      | 1.82              | 0.820     | 0.49              |
| CaCl$_2$                | 0.05                  | 10.41      | $-5.28$           | 0.817     | 0.12              |
| KNO$_3$                 | 0.05                  | 10.87      | $-1.09$           | 0.816     | 0                 |
| BaCl$_2$                | 0.05                  | 10.42      | $-5.29$           | 0.819     | 0.37              |
| Na$_2$SO$_4$            | 0.005                 | 10.89      | $-0.91$           | 0.816     | 0                 |
| Na$_2$-EDTA             | 0.005                 | 10.92      | $-0.64$           | 0.816     | 0                 |
| tropicamide             | 0.005                 | 11.22      | 2.09              | 0.823     | 0.86              |
| dexamethasone sodium phosphate | 0.005         | 10.97      | $-0.18$           | 0.815     | $-0.12$           |
| lincomycin hydrochloride | 0.005                 | 11.11      | 1.82              | 0.820     | 0.49              |

According to reversible electrode reactions, the following relationship exists between the $E_p$ and scan rate [18]:

$$E_p = E^\circ - \frac{RT}{\alpha nF} \left[ 0.78 - \ln \frac{k^0}{D^{1/2}} + \ln \left( \frac{\alpha nFv}{RT} \right)^{1/2} \right],$$

3.8. Electrode precision and repeatability

After obtaining a stable scan in the blank solution, the freshly prepared modified electrode was evaluated by continuously measuring the PHE standard solution 10 times. As the relative standard deviation (RSD) was 0.7%, the modified electrode was highly precise. Seven electrodes were prepared with the same condition at the same time. RSD was 2.9% when measuring the same PHE standard solution, which indicated good repeatability.

3.9. Calibration curve and limit of detection

Under the optimized conditions, CV was selected to determine PHE at MWCNT-CPEs. When the PHE concentration is within 5.0 x 10$^{-6}$–7.5 x 10$^{-4}$ mol l$^{-1}$, there is a good linear relationship (figure 5) between PHE concentration and $I_p$. The linear equation is $I = 5.8764c \times 10^{-4}$ mol l$^{-1}$ + 5.737 ($r = 0.9995$), and based on the signal-to-noise ratio of 3, the detection limit is obtained as 3.7 x 10$^{-7}$ mol l$^{-1}$.
3. Sample analysis

MWCNT-CPE was used to measure PHE injection, eye drops and nasal spray liquid. Referring to table 2 for the measurement results and recovery, it shows that the method is applicable for the determination of PHE in various medicines.

4. Conclusion

A sensitive method of determining PHE with a selective MWCNT-CPE was established. The optimal conditions were as follows: the ratio of MWCNTs was approximately 12.5% (w/w) in the working electrode, PBS at pH 6.45 was chosen as the buffer and the accumulation time was 10 s. With a scan rate of 400 mV s$^{-1}$, PHE exhibited an oxidation peak at 0.816 V. When the concentrations were $5.0 \times 10^{-6} - 7.5 \times 10^{-4}$ mol l$^{-1}$, there was a good linear relationship between PHE concentration and $I_p$, and the detection limit was found to be $3.7 \times 10^{-7}$ mol l$^{-1}$ ($S/N = 3$). The method was applied to detect PHE in different samples, and the results were satisfying. This method features simplicity, speediness and low detection cost using a small, portable electrochemical workstation, and it can be applied for quick on-site detection.

Data accessibility. All data are included in the article.
Authors’ contributions. Y.F.P. designed the study, H.Y.Z. prepared all samples for analysis, Q.Z. collected and analysed the data, and wrote the manuscript. All authors give final approval for publication.
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References

1. Devanajan PV, Adani MH, Gandhi AS. 2000 Simultaneous determination of lignocaine hydrochloride and phenylephrine hydrochloride by HPTLC. J. Pharm. Biomed. Anal. 22, 685–690. (doi:10.1016/S0731-7085(99)00295-2)

2. Dewani AP, Dabhiade SM, Bakal RL, Gadewar CK, Chandewar AV, Patra S. 2015 Development and validation of a novel RP-HPLC method for simultaneous determination of paracetamol, phenylephrine hydrochloride, caffeine, cetirizine and nimesulide in tablet formulation. Arab. J. Chem. 8, 591 – 596. (doi:10.1016/j.arabjc.2013.09.040)

3. Feng S, Zhao Q, Jiang J, Hu P. 2013 Voltammetric determination of nimesulide in tablet formulation. Arab. J. Chem. 8, 791 – 799. (doi:10.1016/S0731-7085(02)00362-X)

4. Shama SA. 2002 Spectrophotometric determination of phenylephrine HCl and orphenadine citrate in pure and in dosage forms. J. Pharmaceut. Biomed. 30, 1385 – 1392.

5. Collado MS, Mantovani VE, Guicochea HC, Olivieri AC. 2000 Simultaneous spectrophotometric-multivariate calibration determination of several components of ophthalmic solutions: phenylephrine, chloramphenicol, atropine, methylparaben and thimerosal. Talanta 52, 909 – 920. (doi:10.1016/S0039-9140(00)00443-4)

6. Marchesi AF, Williner MR, Mantovani VE, Robles JC, Guicochea HC. 2003 Simultaneous determination of naproxenine, diphenhydramine and phenylephrine in nasal solutions by capillary electrophoresis. J. Pharmaceut. Biomed. 31, 39 – 46. (doi:10.1016/S0731-7085(02)00600-3)

7. Gomez MR, Olima RA, Martinez LD, Silva MF. 2002 Simultaneous determination of dextromethorphan, diphenhydramine and phenylephrine in expectorant and decongestant syrups by capillary electrophoresis. J. Pharmaceut. Biomed. 30, 791 – 799. (doi:10.1016/S0731-7085(02)00362-X)

8. Hu CH, Deng J, Xiao XL, Zhan XZ, Huang KH, Xiao N, Ju SQ. 2015 Determination of dimetindazole using carbon paste electrode modified with aluminum doped surface molecularly imprinted siloxane. Electrochim. Acta 158, 298 – 305. (doi:10.1016/j.electacta.2015.01.176)

9. Arvand M, Fallyahi P. 2013 Voltammetric determination of rivastigmine in pharmaceutical and biological samples using molecularly imprinted polymer modified carbon paste electrode. Sensor. Actuat. B-Chem. 188, 797 – 805. (doi:10.1016/j.snb.2013.07.092)

10. Sadeghi S, Motaharian A, Moghadam AZ. 2012 Electroanalytical determination of sulfasalazine in pharmaceutical and biological samples using molecularly imprinted polymer modified carbon paste electrode. Sensor. Actuat. B-Chem. 168, 336 – 344. (doi:10.1016/j.snb.2012.04.033)

11. Liu ZP, Zhai HY, Chen ZG, Zhou Q, Liang ZX, Su ZH. 2014 Simultaneous determination of orange G and orange II in industrial wastewater by a novel Fe3O4/NWNTs-COOH/DP modified carbon paste electrode. Electrochim. Acta 136, 370 – 376. (doi:10.1016/j.electacta.2014.05.090)

12. Zhai HY, Liang ZX, Chen ZG, Wang HH, Liu JP, Su ZH, Zhou Q. 2015 Simultaneous detection of metronidazole and chloramphenicol by differential pulse stripping voltammetry using a silver nanoparticles/sulfonate functionalized graphene modified glassy carbon electrode. Electrochim. Acta 171, 105 – 113. (doi:10.1016/j.electacta.2015.03.140)

13. Liang ZX, Zhai HY, Chen ZG, Wang HH, Wang SM, Zhou Q, Huang XT. 2016 A simple, ultrasensitive sensor for gallic acid and uric acid based on gold microclusters/sulfonate functionalized graphene modified glassy carbon electrode. Sensor. Actuat. B-Chem. 224, 915 – 925. (doi:10.1016/j.snb.2015.10.101)

14. Huang F, Jin GY, Liu Y, Kong JL. 2008 Sensitive determination of phenylephrine and chlorprothixene at poly(4-aminobenzene sulfonic acid) modified glassy carbon electrode. Talanta 74, 1435 – 1441. (doi:10.1016/j.talanta.2007.09.018)

15. Zhu YH, Zhang ZZ, Zhao W, Pang DW. 2006 Voltammetric behavior and determination of phenylephrine at a glassy carbon electrode modified with multi-wall carbon nanotubes. Sensor. Actuat. B-Chem. 119, 308 – 314. (doi:10.1016/j.snb.2005.12.026)

16. Gholivand MB, Malekzadeh G, Torkashvand M. 2013 Enhancement effect of sodium-dodecyl sulfate on the anodic stripping voltammetric signal of phenylephrine hydrochloride at carbon paste electrode. J. Electroanal. Chem. 704, 50 – 56. (doi:10.1016/j.jelechem.2013.06.013)

17. Perlado JC, Zapardiel A, Bermejo E, Pérez JA, Hernández I. 1995 Determination of phenylephrine with a modified carbon paste electrode. Anal. Chim. Acta 305, 83 – 90. (doi:10.1016/0003-2670(94)00441-N)

18. Wang J. 2003 Analytical electrochemistry, 3rd edn, pp. 48 – 49. Hoboken, NJ: Wiley-VCH.

19. Ma HY, Hu NF, Rusing JF. 2000 Electroactive myoglobin films grown layer-by-layer with poly(styrenesulfonate) on pyrolytic graphite electrodes. Langmuir 16, 4969 – 4975. (doi:10.1021/la991296t)