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Differential pulse adsorption voltammetry for determination of procaine hydrochloride at a pumice modified carbon paste electrode in pharmaceutical preparations and urine

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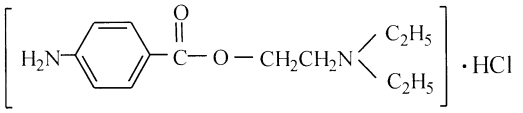
Abstract

Procaine hydrochloride was determined by the differential pulse voltammetry (DPV) using a 6% (m/m) pumice modified carbon paste electrode in 1.25×10^{-3} mol l^{-1} KH_2PO_4 and Na_2HPO_4 buffer solution (pH 6.88, 25 °C). The anodic peak potential used was +0.980 V (vs. SCE). A good linear relationship was realized between the anodic peak current and procaine concentration in the range of 9.0×10^{-7}–2.6×10^{-5} mol l^{-1} with the detection limit of 5.0×10^{-8} mol l^{-1}. The recovery was 95.2–104.8% with the relative standard deviation of 3.2% ($n = 10$). The pharmaceutical preparations, procaine hydrochloride injection and the urine samples were determined with the desirable results.

Keywords: Procaine hydrochloride; Pumice; Carbon paste electrode; Differential pulse voltammetry; Urine

1. Introduction

The molecular structure of procaine is



which is one of the oldest and widely used quick-action local anesthetics with less toxicity than cocaine. The procaine is not effective on intact skin or mucous membranes, but acts promptly when used by infiltration [1]. It must, therefore, be administered intramuscularly to create a depot from which benzylpenicillin is slowly released into the bloodstream [2]. It reversibly blocks impulse conduction along nerve axons and other excitable membranes that utilize sodium channels as the primary means of action potential generation. This action can be used clinically to block pain sensation from specific areas of the body [3]. It penetrates tissues in the form of uncharged molecules and exerts its action intracellularly as cation [4].

The British and United State pharmacopoeial methods for assaying procaine hydrochloride [2] are based on solvent extraction of procaine hydrochloride, followed by either spectrophotomet-

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ric measurement at 280 nm or titration with sodium hydroxide. The Chinese pharmacopoeial method is dead-stop titration [5].

Other techniques for the determination of procaine hydrochloride have been developed including spectrophotometry [4,6,7], gas chromatography [8], liquid chromatography [9,10], fluorimetric detection [11,12], chemiluminescence [13,14] and flow-injection analysis [15].

Some investigations have been focused on the electrochemical method for determination of procaine hydrochloride, including coulometric titration [16] with the titrant of mercuric acetate using a hydrogen-saturated palladium electrode, and potentiometric titration [17]. Wang described a method of amperometric detection for local anaesthetics using liquid chromatography with a metal-oxide dispersed glassy-carbon electrode [18]. Its linear relationship was in the range 2–220 ng of procaine with corresponding detection limits of 1.5 ng. Ogurtov determined procaine in powder, injection formulations and in suppositories by D.C polarography when procaine was reduced at the dropping-mercury electrode in the presence of LiCl as supporting electrolyte ($E_{1/2} = -1.20$ V) [19]. Procaine hydrochloride was also determined by A.C oscilloplarographic titration [20]. However, many of methods mentioned above required several time-consuming manipulation steps, sophisticated instruments and special training. Much attention has been devoted to the prospects of the use of ISEs for the procaine determination [2,21]. Unfortunately, its detection limits was only 10^{-5} mol l^{-1}. For these reasons, the method with high sensitivity enjoying rapid, simple and accurate simultaneously is expected to be established.

Carbon paste electrode has be widely used in determination of drugs, biomolecule, and other organic species because of easy preparation, and wider potential window of -1.4 to $+1.3$ (V vs. SCE) according to the experimental condition. Its residual current is ten times lower than that of the glassy carbon electrodes or noble metallic electrodes [22]. In this paper, pumice was modified into carbon paste for determination of procaine hydrochloride, and a good result was obtained with the detection limit of 5.0×10^{-8} mol l^{-1}. Compared with the ISEs [2,21], the detection limit of this method decreases two orders of magnitude, and its sensitivity is higher than conventional electrochemical method [19,20]. This method enjoys lower interference, rapid and simple operation and high accuracy.

2. Experiment

2.1. Reagents

A stock solution of procaine hydrochloride (1.0×10^{-3} mol l^{-1}) was prepared, and kept in the dark under refrigeration (low 4 °C). All reagents were of analytical grade. All solutions were prepared with double-distilled water. The spectroscopially pure graphite powder was obtained from Shanghai Carbon Factory (China), and the nubby pumice with density of 0.38 g cm^{-3} was obtained from Huzhou Biochemical Factory (China).

2.2. Apparatus

Electrochemical measurements were performed using a 660A CHI (CH Instrument, Ins, USA). A three-electrodes system was used with a pumice modified carbon paste electrode as working electrode, a platinum plate electrode as the counter electrode and a saturated calomel electrode (SCE) as the reference electrode.

2.3. Procedure

2.3.1. Fabrication of pumice modified carbon paste electrode

The pumice modified carbon paste was prepared by carefully mixing 1.0 g of graphite powder, 0.1 g of milled pumice powers (150 screen mesh) and 0.6 g of Nujol oil in a mortar. The carbon paste was packed into the glass syringe (1 ml) the tip end of which was sleeved by a plastics tube with a diameter of 2 mm and length of 4 cm. The tip of piston in the glass syringe was sealed with a platinum wire for electrical conduct. The piston was pushed, 1 mm carbon paste was squeezed out, then scratched and smoothed on the

surface of a piece of glass when the surface of the electrode need renewed. The reproducibility of the electrode was remarkable because its area was small and coincident.

2.3.2. Determination of procaine hydrochloride

The pumice modified carbon paste electrode, the platinum plate counter electrode, and the saturated calomel reference electrode (SCE) were immersed in 20.0 ml of 1.25×10^{-3} mol l^{-1} KH_2PO_4 and Na_2HPO_4 buffer solution (pH 6.88, 25 °C). A certain amount of procaine hydrochloride was added, and the solution was stirred by a magnetic stirrer. The pre-concentration was carried out at +0.0 V for 30 s, and then stopped the stirring for 20 s. The differential pulse voltammetry was immediately performed from 0.0 to 1.3 V at a scan rate of 10 mV s^{-1} with the sampling width of 0.05 s, pulse amplitude of 50 mV, and pulse period of 0.2 s. The anodic peak current at 0.980 V was recorded (Fig. 1). The standard addition method was applied for quantitative determination of procaine hydrochloride concentration. After each determination, the electrode was stirred in 1.25×10^{-3} mol l^{-1} phosphate buffer solution for several minutes at 0.0 V (SCE), and the scan of DPV was simultaneously carried out till there was no peak wave at 0.980 V. Otherwise, the renewal step should be repeated again.

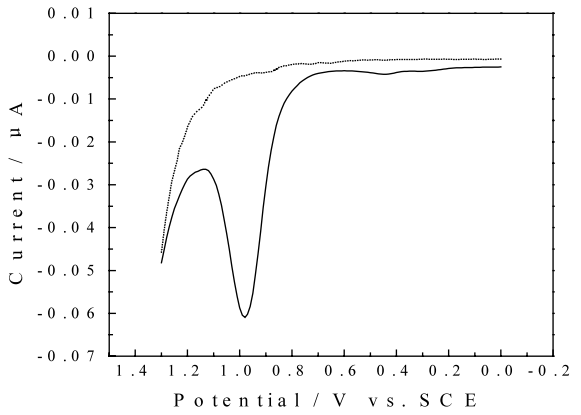


Fig. 1. Differential pulse voltammograms of the pumice carbon paste electrodes in phosphate buffer. Accumulation potential under stirring: 0.0 V, Accumulation time: 30 s, Quiet time: 20 s, pulse height: 0.050 V, sampling width: 0.05 s, pulse period: 0.2 s, sensitivity: 1.0×10^{-7} A/V. Solid line: in 2.0×10^{-6} mol l^{-1} procaine hydrochloride. Short dot line: in absent of procaine hydrochloride.

3. Results and discussion

3.1. Optimization of analysis condition

When the pH value was lower than 6.88, the anodic peak current of procaine would decease and peak potential shift toward positive direction where the interference of water electrolysis became serious. On the other hand, the residual current would increase remarkably in the alkaline solution. The highest sensitivity and fine procaine voltammograms were obtained in 1.25×10^{-3} mol l^{-1} KH_2PO_4–Na_2HPO_4 buffer solution (pH 6.88, 25 °C). Other supporting electrolytes were also tested, such as HCl, H_2SO_4, HAc–NaAc, NH_4Cl–$NH_3 \cdot H_2O$, KCl and $HClO_4$. All of them were not suitable for procaine determination comparing with phosphate buffer. The peak current increased with increase of accumulation time when procaine concentration was low than 5.0×10^{-5} mol l^{-1}. But this increase was ceased when the accumulation time was over 30 s indicating that the procaine adsorption at electrode surface reached saturation.

3.2. The role of the pumice

Pumice (float-stone) is a kind of porous igneous rock composed of intricate silicates, and its density is so very low (0.3–0.8 g cm^{-3}) that it can float on water. Pumice is usually composed of 67–75% SiO_2 and 10–20% Al_2O_3 containing some metal ions, such as K^+, Na^+ and Ca^{2+} etc. It does not dissolve in water or react with conventional acids. Like some clay and zeolite, strong adsorption of pumice due to its porosity was attractive and has been used as catalyst [23,24] and ion exchange [25]. Mixing pumice into carbon paste facilitates electrochemical catalysis of molecules or ions. The pumice carbon paste electrodes also possessed chemical and thermal stability.

The anodic peak currents of procaine and the stability of electrode were considerably related to

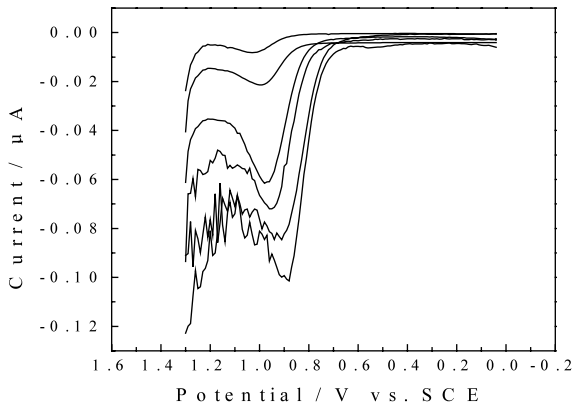


Fig. 2. Differential pulse voltammograms of 2.0×10^{-6} mol l^{-1} procaine hydrochloride with various contents of pumice in carbon paste electrode in phosphate buffer. The descending order of currents are 22, 15, 9, 6, 3 and 0% (m/m) of pumice in carbon paste electrode, respectively.

the content of pumice in carbon paste. The pumice contents of 0, 3, 6, 9, 15 and 22% (m/m) were tested respectively in phosphate buffer solution. It was found that increasing pumice content in the carbon paste would increase the peak current of procaine because of pumice adsorption and the peak potentials would shift towards negative direction that facilitated procaine determination. But the background currents and the electrode resistance increased obviously when the pumice content exceeded 15% (Fig. 2). The optimum content of pumice was 6% for the procaine determination.

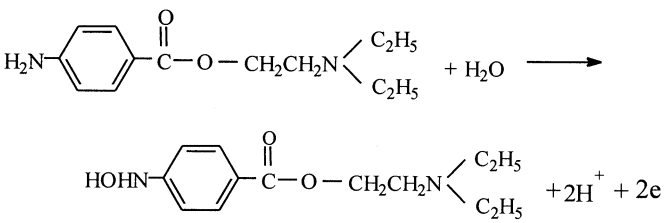
3.3. Reaction mechanisms on the electrode

Experiment results showed that the peak currents of cyclic voltammetry in 2.0×10^{-6} mol l^{-1} procaine solution were proportional to the scan rates v. It implied that the electrode process was a typical surface adsorption process. When procaine concentration exceeded 1.0×10^{-5} mol l^{-1}, the peak currents were proportional to the $v^{1/2}$ indicating that the electrode process was controlled by the diffusion process.

The procaine solution was electrolyzed exhaustively at $+0.980$ V until the electrolytic current was close to zero, and the quantity of electrical charge Q_1 was recorded. Similarly, the background solution was electrolyzed under the same conditions, and the quantity of electrical charge Q_2 was obtained. The charge difference. $Q = (Q_1 - Q_2)$ represents the quantity of electrical charge consumed by procaine:

$$\Delta Q = nFCV \quad (1)$$

C and V here are the concentration and volume of the procaine solution respectively. n and F has their conventional meanings. From Eq. (1) the electron number n of the electrochemical reaction of procaine can be calculated and is equal to 1.95. The pH value strongly affects the peak potential of procaine. It showed that the peak potentials shifted towards positive direction with decrease of pH value. A good linear relationship was obtained between the peak potential and pH value in the range of pH 5.3–9.0 with the slope of 0.0746 which equals 0.059 $m/\beta n$. Here m is the number of H^+ transfer. From above discussion it can be concluded that the redox of a procaine molecule is a process of two H^+ and two electrons. The possible half-reaction is as follows:



3.4. Calibration curve

The anodic peak currents were proportional to procaine concentrations in the range of 9.0×10^{-7}–2.6×10^{-5} mol l^{-1} under the optimum experimental conditions. The linear equation was i_p (μA) $= 0.03143 + 5.062 \times 10^3 C$ (mol l^{-1}) with

the correlation coefficient $r = 0.995$. The calibration curve would deviate from the linear relationship when the procaine concentration was more than 2.6×10^{-5} mol l^{-1}. The detection limit was 5.0×10^{-8} mol l^{-1} (S/N = 3). A further lower detection limit could be obtained by prolonging the time of preconcentration.

3.5. Reproducibility

The 2.0×10^{-6} mol l^{-1} procaine was determined repeatedly with the same electrode for nine times. The average current was 0.0448 μA with the R.S.D. of 2.1%. Then the precision of potential values with the carbon paste electrode renewed after each determination was also measured. The average peak current of 2.0×10^{-6} mol l^{-1} procaine was 0.0445 μA with the R.S.D. of 3.7% ($n = 9$). After 1 year, with the same electrode, the measurement results were in a good agreement. It indicated that the reproducibility of the electrode was remarkable.

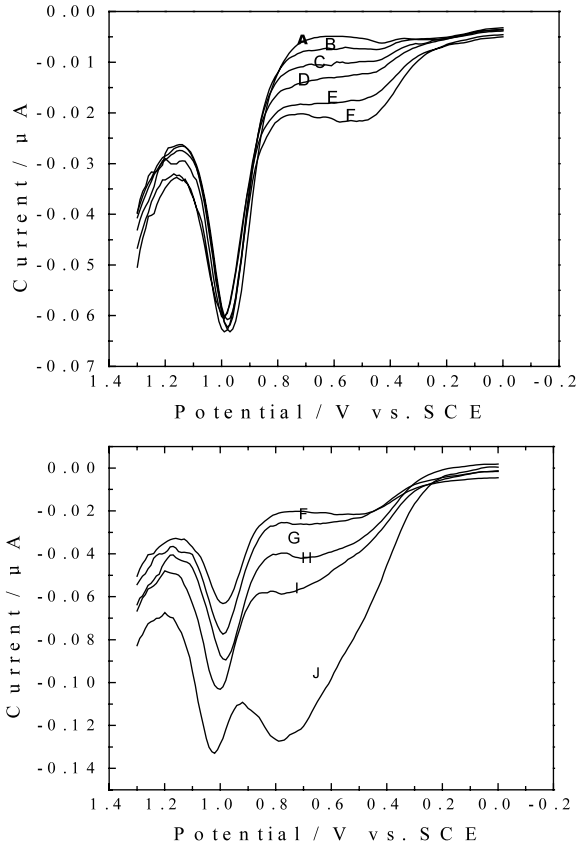


Fig. 3. Differential pulse voltammetry of 2.0×10^{-6} mol l^{-1} procaine hydrochloride in the presence of L-ascorbic acid. (A) Procaine hydrochloride, Ascorbic acid concentration: (B) 2.0×10^{-6} mol l^{-1}, (C) 4.0×10^{-6} mol l^{-1}, (D) 6.0×10^{-6} mol l^{-1}, (E) 1.2×10^{-5} mol l^{-1}, (F) 1.6×10^{-5} mol l^{-1}, (G) 2.0×10^{-5} mol l^{-1}, (H) 4.0×10^{-5} mol l^{-1}, (I) 6.0×10^{-5} mol l^{-1}, (J) 1.0×10^{-4} mol l^{-1}.

3.6. Interference

When 2.0×10^{-6} mol l^{-1} procaine in urine was determined, no interferences were observed in the presence of 2.0×10^{-3} mol l^{-1} of NaCl, KNO_3, $(NH_4)SO_4$, $ZnSO_4$, $Al(NO_3)_3$, $Mg(NO_3)_2$, $Ca(NO_3)_2$, glucose, Oxalic acid, urea, tartaric acid, caffeine, 1.0×10^{-3} mol l^{-1} of cysteine, cystine, DL-tyrosine, glutamic acid, citrate, Malic acid, $CuSO_4$, 2.0×10^{-4} mol l^{-1} of albumin fraction and $Fe(NO_3)_3$. Some conventional medicaments, such as 1.0×10^{-3} mol l^{-1} of salicylic acid, 5-sulfosalicylic acid, Vitamin B_1, Vitamin B_2, Vitamin B_6, atropine, penicillin, amitriptyline, and theine, did not interfere with the determination.

However, ascorbic acid, uric acid, adrenaline and dopamine had some responses at the electrode in the ranges of scan potential. Fig. 3 shows that no interference was observed in presence of 1.6×10^{-5} mol l^{-1} ascorbic acid, and although 4.0×10^{-5} mol l^{-1} ascorbic acid caused the current increase, the peak current of procaine was not affected. The 50 times concentration of ascorbic acid would interfere with the determination. Actually, the content of ascorbic acid in urine of a healthy human is less than 1.0×10^{-5} mol l^{-1}. Figs. 4–6 show the determination of procaine in the presence of uric acid, dopamine and adrenaline respectively all of which did not cause interference with determination of 2.0×10^{-6} mol l^{-1} procaine. Commercially available injection medicines of procaine usually contain ascorbic acid (40 mg of procaine and 100 mg of Vc in 2 ml) or adrenaline (40 mg of procaine and 0.05 mg of adrenaline in 2 ml) [26]. There was obviously no interference with procaine measurement in urine sample that was collected after certain time of injecting this injection. The content of adrenaline or dopamine in normal urine sample is less than

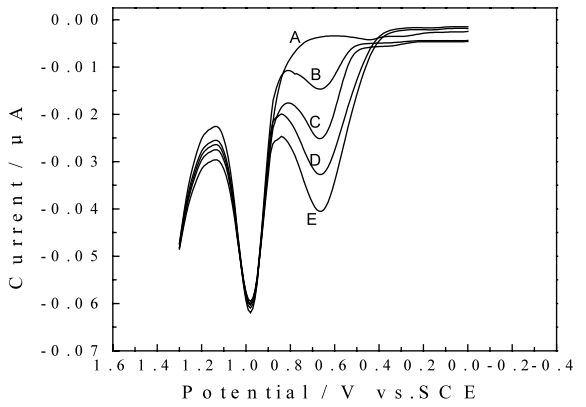


Fig. 4. Differential pulse voltammetry of 2.0×10^{-6} mol l^{-1} procaine hydrochloride in the presence of urine acid. (A) Procaine hydrochloride; Urine acid concentration: (B) 2.0×10^{-5} mol l^{-1}, (C) 6.0×10^{-5} mol l^{-1}, (D) 8.0×10^{-5} mol l^{-1}, (E) 1.0×10^{-4} mol l^{-1}.

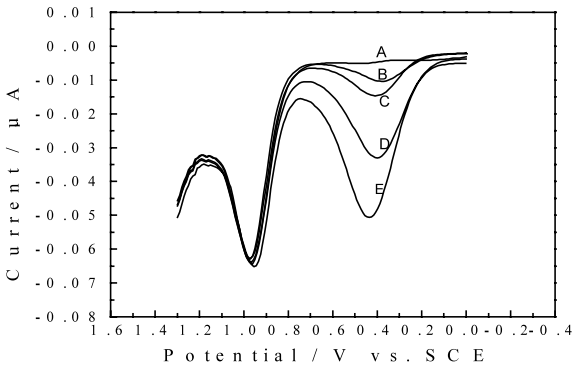


Fig. 5. Differential pulse voltammetry of 2.0×10^{-6} mol l^{-1} procaine hydrochloride in the presence of dopamine (A) Procaine hydrochloride; Dopamine concentration: (B) 2.0×10^{-6} mol l^{-1}, (C) 5.0×10^{-6} mol l^{-1}, (D) 1.0×10^{-5} mol l^{-1}, (E) 2.0×10^{-5} mol l^{-1}.

1.0×10^{-8} mol l^{-1}[26]. But we found the 2.0×10^{-5} mol l^{-1} lignocaine hydrochloride interfered with the determination. We covered the pumice modified carbon paste electrode with cellulose acetate (CA) membrane according to the method Gilmartin reported [27], i.e. 2% m/v CA solution was directly dropped on the electrode surface. It was found that the interference of ascorbic acid at CA modified electrode was more severe than that at the pumice modified carbon paste electrode.

3.7. Determination of the pharmaceutical preparation samples

The recovery tests of procaine ranging from 2.5×10^{-6} to 2.5×10^{-5} mol l^{-1} were performed. The results were listed in Table 1. The recoveries lay in the range from 95.2 to 104.8% and the R.S.D. was 3.2%.

The procaine hydrochloride injection (Xudonghai Pharmaceutical Co. Ltd., China, batch No.

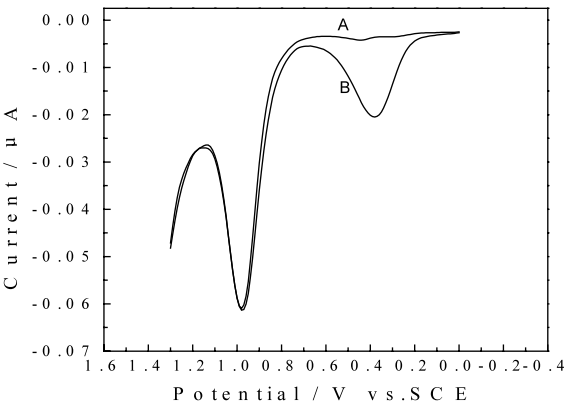


Fig. 6. Differential pulse voltammetry of 2.0×10^{-6} mol l^{-1} procaine hydrochloride in the presence of adrenaline. (A) Procaine hydrochloride; (B) 2.0×10^{-5} mol l^{-1} Adrenaline.

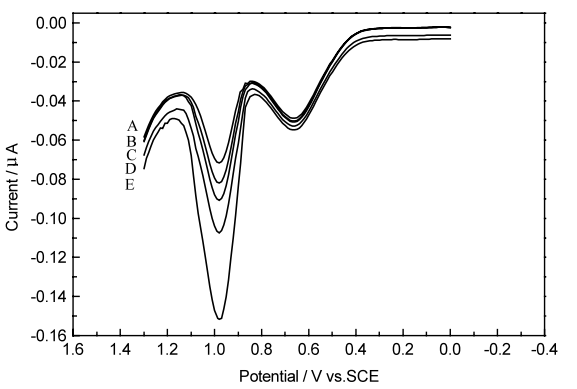


Fig. 7. Differential pulse voltammograms of procaine in urine sample in phosphate buffer. Concentration of procaine: (A) 2.0×10^{-6} mol l^{-1}, (B) 4.0×10^{-6} mol l^{-1}, (C) 6.0×10^{-6} mol l^{-1}, (D) 1.0×10^{-5} mol l^{-1}, (E) 2.0×10^{-5} mol l^{-1}. Accumulation potential: 0.0 V, Accumulation time: 30 s, Quiet time: 20 s, Pulse height: 0.050 V, Sampling width: 0.05 s, Pulse period: 0.2 s, Sensitivity: 1.0×10^{-7} A/V. Another peak at 0.665 V was caused by urine acid.

Table 1
Recovery test of procaine hydrochloride

Added (mol l^{-1})	Found (mol $^{-1}$)	Recovery (%)
2.50×10^{-6}	2.62×10^{-6}	104.8
5.00×10^{-6}	5.10×10^{-6}	102.0
7.50×10^{-6}	7.55×10^{-6}	100.7
1.00×10^{-5}	9.79×10^{-6}	97.9
1.25×10^{-5}	1.27×10^{-5}	101.6
1.50×10^{-5}	1.44×10^{-5}	96.0
1.75×10^{-5}	1.67×10^{-5}	95.4
2.00×10^{-5}	1.97×10^{-5}	98.5
2.25×10^{-5}	2.18×10^{-5}	96.9
2.50×10^{-5}	2.38×10^{-5}	95.2

990901 and 990902) labeled amount of 20 mg ml^{-1} was determined by the present method. The contrast tests were carried out by The Chinese Pharmacopoeial Methods [5]. All results obtained showed in Table 2. A good agreement between two methods was achieved.

3.8. Determination of procaine hydrochloride in urine

An aliquot of original urine was collected. A certain amount of procaine hydrochloride was added into 50.0 ml of urine (the concentration is 1.0×10^{-3} mol l^{-1}), then 0.020 ml of above urine sample was transferred to 20.0 ml solution of KH_2PO_4–Na_2HPO_4 buffer solution (Fig. 7). The procaine hydrochloride concentration in the urine was determined by the multiple standard additions of DPV. Recoveries of procaine hydrochloride were shown in Table 3 in which the proposed method yielded recoveries of 94.7–104.4%.

4. Conclusion

This paper describes a simple and sensitive method for the detection of procaine in the pharmaceutical preparations and urine by differential

Table 2
Determination of the injection samples of procaine hydrochloride

Batch number	Pharmacopoeial method[a]		Presented method	
	Found ($n=3$) 10^{-2} g per 2 ml	R.S.D. (%)	Found ($n=5$) 10^{-2} g per 2 ml	R.S.D. (%)
990901	3.90	2.3	3.88	2.2
990902	3.89	1.9	3.90	2.9
991212	3.86	2.0	3.82	2.5

[a] The data was provided by Yangzhou institute for the control of pharmaceutical products (People's Republic of China).

Table 3
Procaine hydrochloride recoveries in urine using the pumice modified carbon paste electrode

Procaine hydrochloride added (10^{-6} mol l^{-1})	Procaine hydrochloride found (10^{-6} mol l^{-1})	R.S.D. ($n=5$) (%)	Average of recovery (%)
1.0	1.02	4.5	102.0
2.0	1.93	3.6	96.5
4.0	4.03	3.4	100.8
6.0	6.07	3.3	101.2
10.0	9.47	4.7	94.7
12.0	11.4	4.1	95.0
16.0	16.6	3.9	103.7
18.0	17.2	4.6	95.5
20.0	19.5	3.5	97.5
22.0	22.2	4.4	100.9
25.0	26.1	4.1	104.4

pulse voltammetry with a pumice modified carbon paste electrode. Significant advantages have been achieved by the simple fabrication of this electrode, rapid determination, excellent sensitivity and selectivity. The reliability and stability of the pumice modified carbon paste electrode offers a good possibility for extending the technique in routine analysis of procaine hydrochloride in the pharmaceutical preparations and in urine.

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