Potentiometric Determination of Dopamine Using a Solid-Contact ~~Polymer~~ Membrane Ion-Selective Electrode

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A simple solid-contact ion-selective electrode for determination of dopamine was developed. The electrode is fabricated with polymeric membranes incorporating heptakis(2,3,6-tri-o-methyl)-β-cyclodextrin as ionophore and sodium trakis[3,5-bis(trifluoromethyl)phenyl]borate as ionic additive. Using hydrophobic poly(3-octylthiophene) as solid-contact transducer, the sensor displays a stable potential response for detection of dopamine in 2 mM HAc-NaAc buffer solution (pH 4.4) within a wide concentration range of 3.0×10^{-5} M–1.0×10^{-3} M with a sub-Nernstian slope of 43.8 ± 0.5 mV/dec. The detection limit calculated as the intersection of the two slope lines is 1.3×10^{-5} M. The electrode exhibits good selectivity over inorganic ions, pharmaceutical excipients and ascorbic acid. In addition, the electrode shows a stable potential response over a wide pH range of 4.0 to 8.5, fast response time (less than 10 s) and excellent repeatability. The proposed electrode has been successfully applied for direct potentiometric determination of dopamine in pharmaceutical formulation without pretreatment procedures.

Keywords: Solid Contact, Ion-Selective Electrode, Dopamine, β-Cyclodextrin.

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1. INTRODUCTION

Dopamine is known as one of the most important catecholamine neurotransmitters widely distributed in the mammalian brain and central nervous system. The abnormality of dopamine levels may lead to neurological disorders, such as parkinsonism and schizophrenia.[1,2] Moreover, dopamine hydrochloride, a hydrochloride salt of dopamine, is generally applied in clinical treatments of bronchial asthma, cardiac surgery, heart failure, hypertension and renal failures associated with shock episodes.[3] Therefore, a sensitive and selective determination of dopamine is important not only for diagnostics and pathological research in biological fluids, but also for pharmaceutical preparations.

Various techniques have been developed to detect dopamine, such as capillary electrophoresis,[4] high-performance liquid chromatography,[5] spectrophotometry,[6] fluorophotometry[7] and chemiluminescence.[8] However, these techniques have several disadvantages, such as expensive equipment, time-consuming and complex sample pretreatment. Potentiometry and voltammetric methods provide a straightforward alternative due to their simplicity and ordinary instruments. However, the challenge for monitoring the concentration of dopamine using voltammetric methods is the interference from other electroactive species, such as ascorbic acid, which has a similar redox potential to that of dopamine. The electrode surface can be readily fouled by accumulation of products from oxidation of ascorbic acid. Furthermore, homogeneous catalytic oxidation of ascorbic acid by oxidized dopamine is another major interference. Many electrodes for voltammetric determination of dopamine have been fabricated using complex modified procedures to eliminate the interference of ascorbic acid.[9–12] Potentiometric ion-selective electrodes (ISEs) have attracted much interest for directly determining a broad range of cations and anions in clinical, environmental and industrial analysis, due to their attractive features including simple design, small size, low energy consumption and low cost. There have been reported that dopamine can be detected based on the conventional liquid-contact ion-selective electrodes.[13,14]

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However, both of them have limitations resulting from the presence of the inner filling solution, such as the need to work in a vertical position, evaporation of the inner solutions and maintenance requirement.[15] Coated-wire ISEs offered a way to eliminate the influence of the inner solution for detection of dopamine.[16] However, the main drawback of coated-wire ISEs is the poor potential stability resulting from the formation of a thin aqueous layer between electronic conductor and ion-selective membrane.[17] All-solid-state dopamine ion-selective electrode based on conducting polymer polyaniline as ion-to-electron transducer has been developed to improve stable potential.[18] However, polyaniline as ion-to-electron transducer suffer from some disadvantages, such as electrochemical side reactions with redox interferences and high sensitivity to CO_2 and O_2.[19] Conducting polymer poly(3-octylthiophene) (POT) is one of the most promising materials as ion-to-electron transducers, because POT is less electroactive and may not take part in electrochemical side reactions to the same extent as the highly p-doped conducting polymers, such as polypyrrole, polyaniline and poly(3,4-ethylenedioxythiophene).[19] Additionally, POT is highly lipophilic, which may effectively prevent the formation of an internal water layer between the electronic substrate and the ion-selective membrane.[20]

Cyclodextrins are a well-known class of natural host molecules composed of six, seven, or eight glucose units (α, β, or γ-CD, respectively) which are toroidal in shape with a hydrophobic inner cavity and a hydrophilic exterior.[21] The structure is favorable for forming the host-guest inclusion complexes with a variety of suitable sized guest molecules, such as dopamine.[22] It has been reported that the inclusion of dopamine in β-CD can be formed with 1:1 stoichiometry through hydrophobic and hydrogen-bonding interactions. Moreover, the stability of dopamine-β-CD complex is much better than ascorbic acid-β-CD complex. Thus, β-CD was used for the detection dopamine. In addition, to increase the lipophilicity of β-CD, trimethyl-β-CD was used as ionophore in the polymeric membrane based on the three alkyl groups at 2, 3, 6 positions.[23]

In the present work, a simple solid-contact ~~polymer~~ membrane dopamine ion-selective electrode has been developed. Hydrophobic conducting polymer poly(3-octylthiophene) was used as solid contact to eliminate water layer in order to obtain the stable potential response. The potential response, selectivity, repeatability and pH effect of the electrode were investigated in detail.

2. EXPERIMENTAL DETAILS

2.1. Chemicals

High molecular weight poly(vinyl chloride) (PVC), 2-nitrophenyl octyl ether (*o*-NPOE), sodium trakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB) and heptakis

(2,3,6-tri-*o*-methyl)-β-cyclodextrin (trimethyl-β-CD) were purchased from Fluka AG (Buchs, Switzerland). Regioregular poly(3-octylthiophene-2,5-diyl) (POT), dopamine hydrochloride, ($\pm$)-epinephrine hydrochloride and DL-noradrenaline hydrochloride was obtained from Sigma-Aldrich.

All other chemicals were of analytical reagent grade. Deionized water (18.2 MΩ cm specific resistance) obtained with a Pall Cascada laboratory water system was used throughout.

2.2. Preparation of Solid-Contact Dopamine Ion-Selective Electrodes

The membrane components for the solid-contact dopamine ion-selective electrodes are shown in Table I. The membrane cocktail was prepared by dissolving 360 mg of membrane components in 2 mL of tetrahydrofuran (THF).

The glassy carbon (GC, 3 mm in diameter) electrode was polished with 0.05 μm alumina slurries, rinsed with deionized water and then cleaned ultrasonically. POT was added on the bare and clean GC electrode by drop-casting 20 μL of 3.6 mg/mL solution in chloroform. After chloroform evaporated, 50 μL of the membrane cocktail was applied on the top of the POT layer and left to dry for at least 2 h at room temperature. For comparison, coated-disk dopamine ion-selective electrode was prepared by directly dropping the ion-selective membrane on the bare GC electrode. The above-prepared electrodes are denoted as GC/POT/dopamine-ISE and GC/dopamine-ISE, respectively. For all measurements, the electrodes were conditioned overnight in 2 mM HAc-NaAc buffer solution (pH 4.4).

2.3. Potentiometric Measurements

The potentiometric measurements were carried out at room temperature using a CHI660C electrochemical workstation (Shanghai Chenhua Apparatus Co.) with a double junction electrode as reference electrode in the galvanic cell: Hg/Hg$_2$Cl$_2$ (saturated KCl solution)/0.1 M LiOAc|sample solution|ISE membrane/POT/GC. The ion activities were calculated by the modified Debye-Hückel equation: $\log \gamma = -0.511Z^2 \ [\mu^{1/2}/(1 + 1.5 \ \mu^{1/2}) - 0.2 \ \mu]$, where μ is the ionic strength and Z is the valence.[24]

2.4. Electrochemical Impedance Spectroscopy

Electrochemical impedance spectroscopy (EIS) was performed with a conventional three-electrode system comprising a solid-contact working electrode, a platinum wire auxiliary electrode and an Ag/AgCl (3 M KCl) reference electrode at the open-circuit potential in the frequency range from 100 kHz–10 mHz by using a sinusoidal excitation signal. An excitation amplitude of 100 mV was

Table I. Membrane compositions of three different solid-contact dopamine ion-selective electrodes.

Electrode type	Ionophore (1.0 wt%)	Ion additives (1.0 wt%)	Plasticizer (65.3–66.0 wt%)	Immobilized matrix (32.7–33.0 wt%)
A	Trimethyl-β-CD		NPOE	PVC
B		NaTFPB	NPOE	PVC
C	Trimethyl-β-CD	NaTFPB	NPOE	PVC

applied for the GC/dopamine-ISE and GC/POT/dopamine-ISE electrodes in order to enhance the signal/noise ratio in 2 mM HAc-NaAc buffer solution (pH 4.4).

3. RESULTS AND DISCUSSION

3.1. Potentiometric Response of the Solid-Contact Dopamine Ion-Selective Electrode

The influence of the membrane composition on the potential response of solid-contact dopamine ion-selective electrodes was investigated and the results are shown in Table II. It can be seen that the potential response of electrode B with the ionic additive is much better than that of electrode A with the ionophore alone, which is due to the fact that the addition of lipophilic salts or ionic additive can decrease the membrane resistance, reduce anion interference, improve the response slope and selectivity of the electrodes.[25] Electrode C with both trimethyl-β-CD and the ion exchanger shows a wider linear range and a lower detection limit than the other types of the electrodes. Figure 1 shows the calibration curve of electrode C in the linear range of 3.0×10^{-5} M–1.0×10^{-3} M in 2 mM HAc-NaAc buffer solution (pH 4.4) with a sub-Nernstian slope of 43.8 mV/dec. The detection limit calculated as the intersection of the two slope lines is 1.3×10^{-5} M, which was much lower than that of other reported potentiometric dopamine sensors.[18, 26] The electrode C also shows a short response time (less than 10 s, see inset of Fig. 1). In addition, the electrode C exhibits good repeatability with less than 5% relative standard deviation ($n = 5$) when successively measured the alternating potential response between a blank solution and 10^{-4} M dopamine using the same electrode.

The long-term response behavior of the electrode C is shown in Figure 2. Between measurements the electrode was kept in the 2 mM HAc-NaAc buffer solution (pH 4.4). It was found that the loss of the detection limit was less
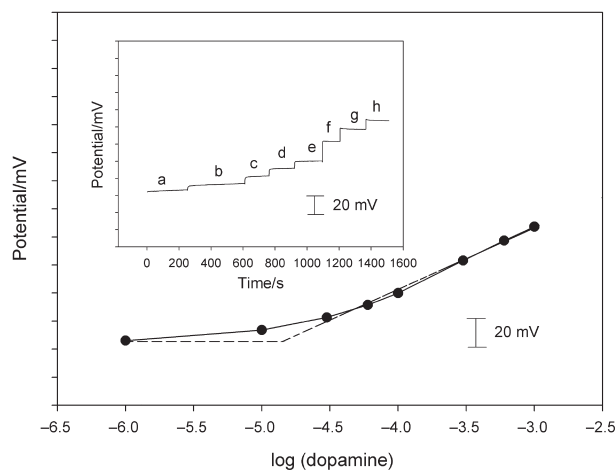

Fig. 1. Calibration curve obtained with the electrode C in 2 mM HAc-NaAc buffer solution (pH 4.4). Inset: Time traces of potential response of electrode C. Concentrations of dopamine (a)–(h): 10^{-6}, 10^{-5}, 3×10^{-5}, 6×10^{-5}, 10^{-4}, 3×10^{-4}, 6×10^{-4} and 10^{-3} M.

than 0.5 orders of magnitude of activity values after a period of 18 days and the slope of the electrode above 6×10^{-5} M dopamine was slightly changed.

3.2. Selectivity

The selectivity of the electrode B and C was performed by using separate solution method (SSM) to eliminate the influence of the inherent sensitivity limit on the response toward discriminated ions.[27] Figure 3 shows the potentiometric selectivity coefficients ($\log K_{DA, J}^{POT}$) of the electrodes B and C from main inorganic cations present in biological fluids and two other catecholamines (adrenaline and noradrenaline) having similar chemical structures to dopamine. It has been found that the selectivity coefficients of electrode C are better than that of electrode B, which is attributed to the host-guest effect between trimethyl-β-CD and dopamine through hydrophobic and

Table II. General characteristics of the solid-contact dopamine ion-selective electrodes.

	Electrode type		
Parameter	A	B	C
Slope (mV/dec)	12.3 ± 0.2	44.2 ± 0.6	43.8 ± 0.5
Linear range (mol/L)	$6.0 \times 10^{-4} - 1.0 \times 10^{-3}$	$5.0 \times 10^{-5} - 1.0 \times 10^{-3}$	$3.0 \times 10^{-5} - 1.0 \times 10^{-3}$
Detection limit[a] (mol/L)	$(1.9 \pm 0.1) \times 10^{-4}$	$(1.8 \pm 0.2) \times 10^{-5}$	$(1.3 \pm 0.2) \times 10^{-5}$
Response time (s)	< 10	< 10	< 10
Linear correlation coefficient (R) ($n = 3$)	0.9992 ± 0.0003	0.9981 ± 0.0008	0.9973 ± 0.0005

Note: [a]The detection limit was calculated from the intersection of two extrapolated segments of the calibration curve.
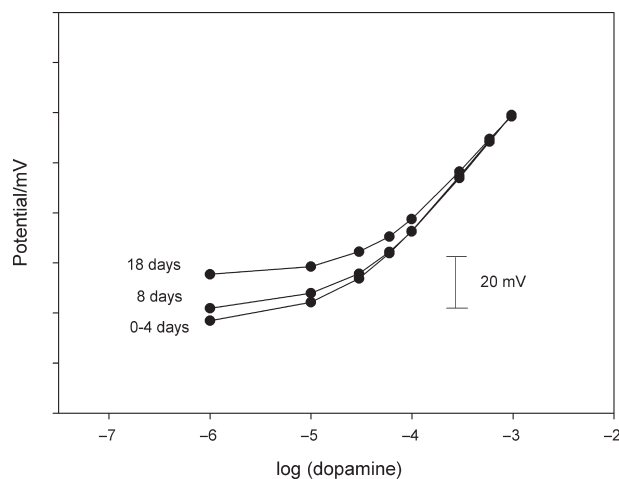
Fig. 2. Long-term response behavior of the electrode C in 2 mM HAc-NaAc buffer solution (pH 4.4).

Fig. 4. Effect of pH on the potential responses of 10^{-4} and 6×10^{-4} M dopamine.

hydrogen-bonding interactions. Figure 3 also shows that the selectivity of the electrodes to adrenaline is worse than that to noradrenaline. This is due to the fact that adrenaline has a methyl ($-CH_3$) group on the nitrogen atom, which may enhance the lipophilicity and favor the incorporation in the polymeric membrane. In addition, pharmaceutical excipients and diluents commonly used in drug formulation (e.g., glucose, lactose and maltose) at concentrations as high as 500-fold molar excess over dopamine concentration did not interference. Moreover, the interference of ascorbic acid was also investigated using the proposed electrode. The potential response hardly changed during the addition of ascorbic acid. The reason is that dopamine ($pK_a = 9.07$)[28] is in the cationic form, while ascorbic acid ($pK_a = 4.10$)[22] exists in the anionic form in 2 mM HAc-NaAc buffer solution (pH 4.4), and the lipophilic anionic additive can effectively reduce anion interference. Therefore, according to the simple mechanism, dopamine can be efficiently detected using the solid-contact cation-selective electrode without the interference of ascorbic acid.
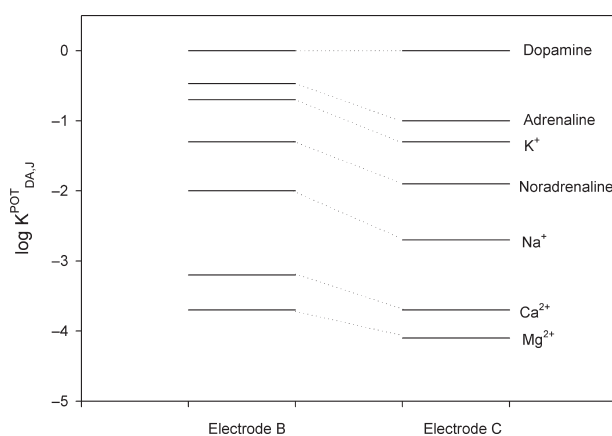
3.3. Effect of pH

The effect of pH on the potential response of the electrode C was estimated in 10^{-3} M $NaNO_3$ with a constant ionic strength. The pH of the solution was adjusted using HNO_3 or NaOH. The results of the pH-potential profile for 10^{-4} and 6×10^{-4} M dopamine using the electrode C are shown in Figure 4. It can be seen that the potential response remains almost constant over a wide pH range of 4.0 to 8.5. However, at pH < 4.0, the potential response decreases, probably due to the interference from protons ions.

3.4. Impedance of the Solid-Contact Dopamine Ion-Selective Electrode

Coated-wire ion-selective electrodes, which were fabricated by directly dropping ion-selective membranes on electronic electrodes, suffer from the long-term potential drift resulting from the high charge-transfer resistance and low double-layer capacitance at the blocked interface between the electronic conductor and ion-selective membrane.[29] Therefore, it's necessary to characterize the interfacial properties of the solid-contact ion-selective electrodes in order to obtain stable potential response. Here, electrochemical impedance spectroscopy was used to probe the interfacial characterizations of the GC/dopamine-ISE and GC/POT/dopamine-ISE.[30] Figure 5 shows the impedance spectra of the GC/dopamine-ISE and GC/POT/dopamine-ISE in 2 mM HAc-NaAc buffer solution (pH 4.4). It can be seen that compared with the GC/dopamine-ISE electrode, the GC/POT/dopamine-ISE electrode exhibits higher low-frequency capacitance and lower charge-transfer resistance because of POT as solid-contact transducer, which is characteristic for "unblocked" interface. The phenomenon is favorable to obtain the stable potential response of the solid-contact dopamine ion-selective electrode.

Fig. 3. Potentiometric selectivity coefficients ($\log K_{DA,J}^{POT}$) of the electrodes B and C determined by separate solution method (SSM).
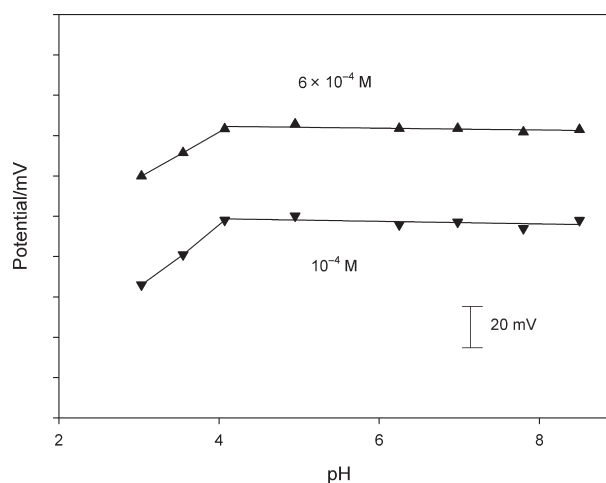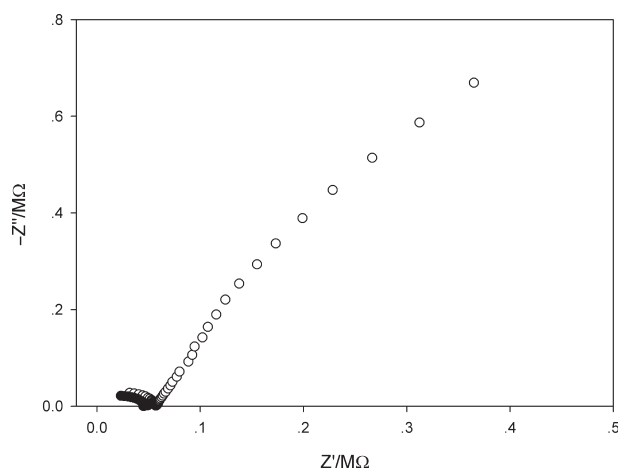
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Fig. 5. Impedance spectra of the GC/dopamine-ISE (hollow circle) and GC/POT/dopamine-ISE (solid circle) electrodes in 2 mM HAc-NaAc buffer solution (pH 4.4) at the open-circuit potential. Frequency range, 0.1–100 kHz; Excitation amplitude, 100 mV.

Table III. Recovery for the determination of dopamine in pharmaceutical preparations using the solid-contact dopamine ion-selective electrode.

	Dopamine hydrochloride injection[a]		
Sample	Added (mg/L)	Found[b] (mg/L)	Recovery (%)
1	9.5	9.7 ± 0.6	102.1
2	19.0	18.8 ± 0.2	98.9
3	95.0	93.1 ± 1.6	98.0

Note: [a]Wuhan Jiuan Pharmaceutical Co., Ltd., China. b. Mean of three determinations ± standard deviation.

3.5. Analytical Applications

To test the feasibility of the solid-contact dopamine ion-selective electrode, injections of dopamine hydrochloride in a commercially available preparation were detected using direct potentiometry. Dopamine hydrochloride injection was diluted with 2 mM HAc-NaAc buffer solution (pH 4.4) to satisfy the concentration of analyte within the range of calibration curve. As shown in Table III, the results obtained by the proposed sensors are in good agreement with the claimed contents and the favorable recoveries are obtained.

4. CONCLUSIONS

A simple solid-contact ~~polymer~~ membrane ion-selective electrode for detection of dopamine has been successfully developed. The electrode shows a stable sub-Nernstian characteristic in 2 mM HAc-NaAc buffer solution (pH 4.4) within a wide concentration range of 3.0×10^{-5} M–1.0×10^{-3} M dopamine with a slope of 43.8 ± 0.5 mV/dec and the practical detection limit is 1.3×10^{-5} M. The electrode has a fast response time (less than 10 s), excellent repeatability and good selectivity over inorganic ions, pharmaceutical excipients and ascorbic acid. Moreover, the electrode

displays a stable potential response over a wide pH range of 4.0 to 8.5. The electrode has been successfully applied to direct determination of dopamine in pharmaceutical formulation without pretreatment procedures. The proposed electrode provides a simple, fast, accurate and precise method for detection of dopamine. Additionally, the use of the solid-contact ion-selective electrode is more durable and easier to miniaturize, as compared to the conventional liquid-contact ion-selective electrodes.

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