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Potentiometric Determination of Salbutamol using Carbon Paste Electrode Assisted with Multi-Walled Carbon Nanotubes

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Abstract- Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). In this work a salbutamol selective nanocomposite sensor based on ion-pair as a sensing element, multi-walled carbon nanotubes (MWCNTs), graphite powder and paraffin oil is constructed. The optimized composition of 7% MWCNTs, 20% Ionophore, 20% paraffin oil and 53% graphite powder shows a Nernestian response of 29.1±0.4 in the range of 5×10^{-6}-1×10^{-2} mol L^{-1}. Multi-walled carbon nanotubes are used because of electrical conductivity and remarkable mechanical strength. The proposed carbon paste electrode can be used over the pH range of 3.5–10 and has a detection limit of 3.0×10^{-6} mol L^{-1}. This method is used to salbutamol recognition in pure solutions and pharmaceutical preparations with high accuracy and precision.

Keywords- Carbon paste electrode, Multi Walled Carbon Nanotube, Potentiometry, Salbutamol

1. INTRODUCTION

Drugs for treating asthma are divided into two categories: (1) Quick-relief medications (which are used to relief acute asthma) and (2) Long-term asthma control medications with (which are used as prophylactic measures). These medications relax the muscle bands that

tighten around the airways. This action rapidly opens the airways, letting more air in and out of the lungs and improving breathing. Bronchodilators also help clear mucus from the lungs. As the airways open, the mucus moves more freely and can be coughed out more easily. In short-acting forms, bronchodilators relieve or stop asthma symptoms and are very helpful during an asthma episode. In long-acting forms, bronchodilators provide control of asthma symptoms and prevent asthma episodes [1]. Salbutamol sulfate (Sl_2SO_4), 1-(4-hydroxy-3-hydroxyphenyl)-2-*tert*-butyl amino ethanol sulfate (Fig. 1) is a highly selective β_2-adrenergic receptor stimulating drug that has a bronchodilator effect; thus, used to prevent and treat wheezing, shortness of breath, coughing, and chest tightness caused by lung diseases such as asthma and chronic obstructive pulmonary disease; a group of diseases that affect the lungs and airways. It can be used safely for patients suffering from heart diseases or hyper tension [2,3].

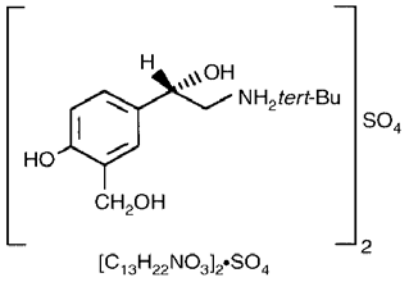

Fig. 1. Structural formula of Sl_2SO_4

Sl_2SO_4 has been determined by several techniques, including HPLC, HPLC-MS, GC-MS, electro kinetic chromatography, MS, LC, immunoassay, capillary electrophoresis, spectrophotometry, voltammetry, and polarography [4-20].

Carbon-based electrodes are currently in widespread use in electroanalytical chemistry, because of their broad potential window, low cost, rich surface chemistry, low background current, chemical inertness, and congruity for a lot of difficult applications. Electroanalytical techniques with carbon-based electrodes are also used in discovery of new drug compounds [21].

Carbon paste electrodes are mixtures prepared from graphite powder and various water-immiscible organic liquids of nonelectrolytic character. After thorough mixing, the paste is packed into a small inert holder (usually 2–5 mm deep, 3 mm diameter and teflon) with electrical contact at the back. The teflon face of the electrode should be flat and smooth. This kind of face guaranties reproducible results. In fact, a major reason for developing carbon paste electrodes was the ease of surface renewal and reproducibility. Physicochemical properties of carbon pastes are always mirrored in the overall electrochemical behavior of the carbon paste electrodes [22-26].

Recently in order to signal improvement, various types of nanomaterials are used in electrochemical sensors. Among them Carbon nanotubes (CNTs) are one of the most exciting materials because of their unique electronic, chemical, and mechanical properties. Currently, multi-walled carbon nanotubes (MWCNTs) have been used in composition of carbon paste electrodes [27–32] because of their interesting and extraordinary physicochemical properties, such as an ordered structure with high aspect ratio, ultra-light weight, high thermal conductivity, metallic or semi-metallic behavior, high surface area, high electrical conductivity and remarkable mechanical strength.

2. EXPERIMENTAL

2.1. Materials and Reagents

Phosphomolybdic acid (PMA) (Merck Co., Germany), Pure grade salbutamol sulfate (Sl_2SO_4), citalopram and pantoprazole were provided by Alborz Company for Pharmaceuticals, Alborz, Ghazvin, Iran. Graphite powder with <52 μm particle size (Merck Co., Germany) and 2.2 g/cm^3 density along with the paraffin oil (Sigma) of the highest purity were used for the preparation of the carbon pastes. MWCNTs with 3-6 μm (Sigma) was used. Acetonitrile and potassium dihydrogen orthophosphate for HPLC analysis were purchased from Merck. All materials were of analytical grade and the highest available purity without further modification.

2.2. Preparation of the ion-pair complex

The ion-exchanger, salbutamolium phosphomolybdate (Sl-PMA) (yellowish green crystals), were prepared by the addition of 150 mL of 10^{-2} mol L^{-1} salbutamol sulfate solution to 100 mL of 10^{-1} mol L^{-1} of phosphomolybdic acid, respectively. The precipitates were filtered, washed thoroughly with distilled water until sulfate free and air dried [33].

2.3. Preparation of the carbon paste electrodes

The carbon paste electrode was prepared as follow: different amounts of ion-pair (Sl-PMA) along with appropriate amounts of graphite powder, paraffin oil, and MWCNTs were totally mixed until completely homogenous paste prepared. The resulting mixture was transferred into a teflon tube of i.d. 5 mm and a height of 3 cm. The paste was packed carefully into the tube tip to avoid possible air gaps. A copper wire was inserted into the opposite end to establish electrical contact. The external electrode surface was smoothed with soft paper. A new surface was produced by scraping out the old surface and replacing the carbon paste. The electrode was finally conditioned for 24 h by soaking in a 1.0×10^{-3} mol L^{-1} salbutamol sulfate solution.

2.4. Apparatus and emf measurements

The electrochemical cell can be represented as follows:

Ag, AgCl(s), KCl (3 mol L^{-1}) || sample solution | carbon paste electrode

All experiments were performed at 25 °C and in salbutamol solutions. A pH/mV meter (Denver, Germany) was used for the potential measurements at 25.0±0.1 °C. The measurements were conducted from low to high concentration of salbutamol. Calibration graph was drawn by plotting the potential, E, versus log [salbutamol].

3. RESULTS AND DISCUSSION

3.1. Composition of the Sensor

Different carbon paste compositions, as shown in Table 1, were prepared. The effect of the paste composition on the potentiometric response of the electrodes was investigated by varying the amounts of the (Sl-PMA) and MWCNTs. It is obvious that the CPEs which were fabricated with MWCNTs revealed better responses Compared with those who did not use it. As it was discussed earlier using MWCNTs in the composition of the carbon paste improves the conductivity of the sensor; By increasing the conductivity, it enhances the dynamic working range and potential response of the sensor [34].

Table1. The optimization of the carbon paste ingredients

No.	Graphite (Wt. %)	Paraffin (Wt. %)	Ion-pair (Wt. %)	MWCNT (Wt. %)	Slope (mV/decade)	Linear Range (mol L^{-1})
1	65	20	15	0	9.5±0.5	1.0×10^{-5} -1.0×10^{-2}
2	60	20	15	5	11.4±0.3	1.0×10^{-5} -1.0×10^{-2}
3	58	20	15	7	14.3±0.4	1.0×10^{-5} -1.0×10^{-2}
4	62	20	18	0	13.2±0.2	5.0×10^{-6} -1.0×10^{-2}
5	57	20	18	5	16.2±0.6	5.0×10^{-6} -1.0×10^{-2}
6	55	20	18	7	18.1±0.5	5.0×10^{-6} -1.0×10^{-2}
7	55	20	20	5	24.2±0.3	5.0×10^{-6} -1.0×10^{-2}
8*	53	20	20	7	29.1±0.4	5.0×10^{-6} -1.0×10^{-2}
9	51	20	22	7	29.0±0.5	5.0×10^{-6} -1.0×10^{-2}
10	52	20	20	8	28.9±0.3	5.0×10^{-6} -1.0×10^{-2}

The ion-exchanger, salbutamolium phosphomolybdate (Sl-PMA) which is embedded in the composition of the sensor acts as sensing element. Phosphomolybdate makes fixed anionic sites and salbutamolium cations can move from solution to these sites in electrode surface depending on the concentration of drug. The higher the concentration, the potential difference is greater. According to the Nernst equation the slope of calibration curve is depended on the charge of salbutamolium cations. As it is seen from Table 1, the electrode No.8 (Starred) with nernstian slope of 29.1±0.4 was selected as the optimal CPE ingredient

composition. So the CPE 8 composition was used in the further studies. For all the electrodes, the standard deviation values were calculated for 3 replicate potential measurements.

3.2. Calibration curve and Statistical Data

The response of the optimal CPE was tested across salbutamol concentration range of 1.0×10^{-6}–1.0×10^{-2} mol L^{-1}. The linear dynamic range of an ion selective electrode is defined as the activity range between the upper and lower detection limits. The applicable range of the proposed sensor extends from 5.0×10^{-6}–1.0×10^{-2} mol L^{-1} (Fig. 2).

The detection limit of an ion selective electrode can be calculated by extrapolating based on the linear portions of the electrode's calibration curve. In this work, the detection limit of the proposed electrode was 3.0×10^{-6} mol L^{-1}.

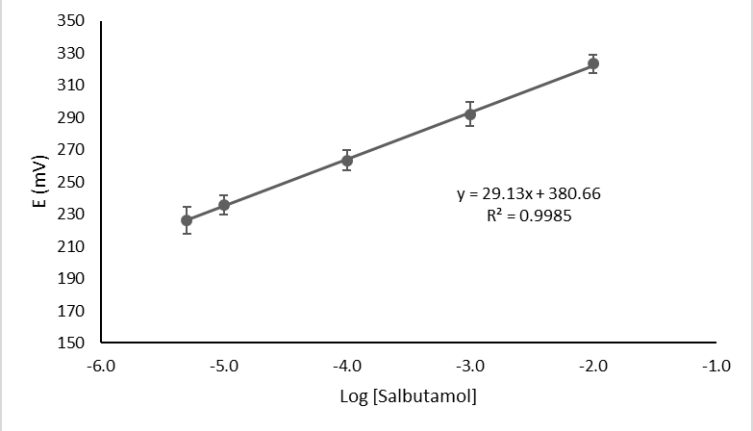

Fig. 2. Calibration curve of Carbon paste electrode The error bar is the standard deviation (SD, n=3).

3.3. pH effect

The effect of pH on the response of the sensor was investigated by monitoring the potential shown by the electrode in a fixed concentration of salbutamol solution (1.0×10^{-4} mol L^{-1}). The pH of the solutions was varied from 2 to 12 by adding very small drops of concentrated HCl or NaOH solutions. The potential changes as a function of pH is shown in Fig. 3. As can be seen, the response of the sensor for 1.0×10^{-4} mol L^{-1} solution of salbutamol is independent of the pH in the range of 3.5-10 and there is no visible interference from H^+ or OH^- in this pH range. At pH lower than 3.5 potential increased, most probably due to further protonation of salbutamol and also the interference of hydronium ions on the ion pair complex. On the other hand, decrease in potentials above pH 10 might be due to the formation of the deprotonated salbutamol species which was not sensed by the CPE.

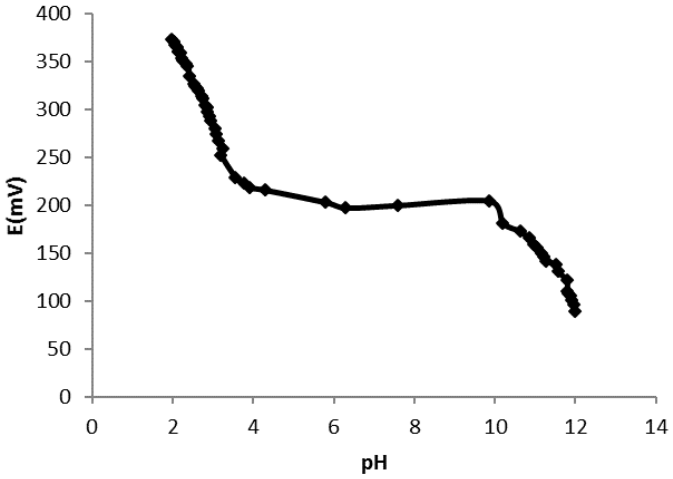

Fig. 3. Effect of the pH of 1×10^{-4} mol L^{-1} salbutamol solution on the potential response of the electrode

3.4. Response Time

Dynamic response time is an important factor for any ion selective electrode. In this study, the practical response time was recorded by using solutions with different salbutamol concentrations. The measurement sequences was from the lower (5.0×10^{-6} mol L^{-1}) to the higher (1.0×10^{-2} mol L^{-1}) concentrations [35]. The average response time was about 20 s.

Table 2. Selectivity coefficients of various interfering compounds

Drug or Ion	**Log (K^{MPM})**
Na^+	-2.01
Mg^{2+}	-3.3
Ca^{2+}	-3.17
Cl^-	-3.12
I^-	-3.03
NO_3^-	-3.43
CH_3COO^-	-3.22
citalopram	-2.13
Pantoprazole	-2.02

3.5. Selectivity of the sensor

Potentiometric selectivity coefficient, which is a measure of preference of the proposed electrode for primary ion A (salbutamol), relative to an interfering ion B, was determined by the matched potential method (MPM), recommended by IUPAC to overcome the difficulties associated with the methods based on the Nicolsky-Eisenman equation [36,37]. As can be seen, for the ions and drugs tested, there are negligible interferences in the performance of the electrode.

3.6. Lifetime

Since the proposed CPE electrode do not contain any plasticizer or membrane solvent, it is more durable and less toxic than the plasticized PVC membranes. The lifetime of the proposed electrode was studied by periodically recalibrating in the standard salbutamol solutions. No significant change in the electrode performance was observed during three months.

Table 3. Salbutamol determination in tablet formulations by the proposed sensor and the official chromatographic method

Sample	Claimed value (mg/tablet)	Amount added (mg)	Found (mg) Potentiometric	Found (mg) HPLC	t-Test (2.78)
Tablet	2	-	2.2±0.4 (n=3)	2.1±0.3 (n=3)	0.35
Tablet	2	5	7.3±0.5 (n=3)	7.2±0.2 (n=3)	0.32

3.7. Analytical applicability

3.7.1. Analysis of salbutamol tablets

The proposed potentiometric procedure was successfully applied for the salbutamol determination in tablets. Using the calibration curve procedure, the resulting data, were statistically compared with the labeled amounts on the tablets and those obtained by the chromatographic method [38] (Table 3).

3.8. Comparison of the proposed electrode with other CPEs

In table 4, merits of the proposed sensor were compared with those of some other CPEs based on ion-pairs for potentiometric determination of drugs. As can be seen the characteristics of the sensors are comparable.

Table 4. Comparison of the characteristics of the proposed electrode with those of the previously reported CPEs based on ion-pair for potentiometric determination of drugs

Analyte	Detection limit ($molL^{-1}$)	Dynamic range ($molL^{-1}$)	Working pH range	Respons e time (s)	Slope (mV/decade)	Ref.
Letrozole	1.0×10^{-6}	1.0×10^{-6}-1.0×10^{-2}	2-5	15 s	19.7±0.3	[39]
Gallamine	1.0×10^{-6}	2.0×10^{-6}-1.0×10^{-3}	5-8	20-45 s	17.0±0.7	[40]
Dicylomine	7.2×10^{-7}	1.2×10^{-5}-1.6×10^{-2}	2-5	~50 s	58.0±2	[41]
Naphazoline	1.5×10^{-6}	1.0×10^{-6}-1.0×10^{-2}	3-8	~30 s	55.9±1.6	[42]
Salbutamol	3.0×10^{-6}	5.0×10^{-6}-1.0×10^{-2}	3.5-10	~20 s	29.1±0.4	This work

4. CONCLUSION

In this study a carbon paste electrode for the salbutamol determination is provided. Using MWCNTs in the composition of CPE improved the potential response of the electrode. The sensor exhibited linear response over a wide concentration range of 5.0×10^{-6}-1.0×10^{-2} mol L^{-1} with a Nernstian slope of 29.1±0.4 mVdecade^{-1} and low detection limit of 8×10^{-6} mol L^{-1}. The proposed sensor can be used in the wide pH range of 3.5-10 and reveals good selectivity for salbutamol against some other drugs and ions. It has fast response time about 20s and long lifetime of three months. The electrode was successfully applied to salbutamol assessment in pharmaceutical samples.

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