A novel coated silver ketamine(I) electrode for potentiometric determination of ketamine hydrochloride in ampoules and urine samples

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ABSTRACT

A new ketamine coated silver electrode (KCSE) based on ketamine hydrochloride with sodium tetraphenylborate (KT-TPB) as electroactive material has been described. The influence of membrane composition, type of solvent mediators, kind of electroactive materials and interfering ions on the sensor was investigated. The sensor displays Nernstian response of 55.8 ± 0.3 mV/decade over the concentration range of 2.5×10^{-6} to 1.0×10^{-2} M with limit of detection of 8.5×10^{-7} M. The coated wire electrode has short response time ~ 8 s and it can be used in pH range of 2.6–6.4. The selective coefficients were determined in relation to several inorganic, organic ions, sugars and some common drug excipients. The KCSE electrode was successfully used for the determination of the ketamine content in ampoule and urine samples with satisfactory results. Statistical student's t-test and F test showed insignificant systematic error between proposed and official methods.

1. Introduction

The development of efficient ion-selective electrodes (ISEs) has always been a big challenge for the scientists as these sensors can be involved nowadays in many fields [1–10]. ISEs were found effective in analysis of pharmaceutical formulations [1,7,9,11–13] for their attractive properties of simple design, ease of construction, reasonable selectivity, fast response time, applicability to colored and turbid solutions and possible interfacing with automated and computerized systems [1].

In conventional polymeric membrane ion-selective electrodes (ISEs), the sensing membrane is interposed between two aqueous phases, the sample and the inner solution. These electrodes, however, still have certain inherent limitations. They are mechanically complicated, and thus difficult to fabricate in small size. In addition, the flux of ions from the membrane, in contact with the inner electrolyte solution that contains a salt of the primary ion, toward

the sample causes the concentration in the contacting aqueous layer to be ca. 10^{-6} M. Consequently, the lower detection limit was found to be around 10^{-6} M [14–16].

One strategy to overcome this drawback is elimination of the inner solution by using a solid inner contact. In a solid-contact or "coated wire" ISE, the polymer membrane is directly cast on the solid surface, with no internal reference solution being interposed. This type of sensors eliminated the internal filling solution provides new advantages, for instance, good mechanical stability, simplicity, and possibility of miniaturization [17].

Ketamine, (2-chlorphenyl)-2-(methylaminocyclohexanone), is a colorless, odorless, tasteless, hallucinogenic and anesthetic commonly used for animals and human. It is used by youth in recreational parties for sedation and misused in drug-facilitated crimes for its pharmacological properties [18]. Ketamine (KT) is metabolized to norketamine (NK) which is then dehydrogenated to dehydronorketamine (DHNK). KT, NK and DHNK are hydroxylation and conjugated before elimination. A mixture of the drug and its metabolites are excreted. KT and NK are the target analytes in toxicological analysis and DHNK is a biomarker of administration of KT in the literature [18,19].

Thus, there is critical need for the development of selective, inexpensive diagnostic tool for the determination of this analyte.

Several analytical methods for the determination of KT are known such as electrochemical method [20], micellar electrokinetic chromatography (MEC) [21], gas chromatography with flame-ionization detector (GC-FID) [22], nitrogen–phosphorus detector (GC-NPD) [23], high-performance liquid chromatography (HPLC) [24], gas chromatography–mass spectrometry (GC–MS) [25,26], liquid chromatography–mass spectrometry (LC–MS) [27,28] and solid-phase extraction (SPE) [29–31]. In addition, poly vinylidene difluoride (PVDF) filter syringes [32] and solid-phase microextraction (SPME), liquid-phase micro extraction (LPME) [22,33] as well as potentiometric methods [34] are in use.

However, most of these methods require sample manipulations that are liable to various interferences as well as being not applicable to colored and turbid solutions. Furthermore, these methods are expensive for they require large infrastructure backup and qualified personnel. Thus, the development of selective and inexpensive diagnostic tool for the determination of this analyte is badly needed.

Analytical methods based on potentiometric detection with ion-selective electrodes (ISEs) can be considered good alternatives for their attractable characteristics mentioned above. Coated wire ion-selective electrodes have been successfully applied as potentiometric sensors for determination of various drugs [1,7,13].

No potentiometric coated wire ion-selective electrode is found for the determination of ketamine hydrochloride on careful review of literature.

In this work, a new ketamine coated silver electrode based on KT-TPB as electroactive materials was prepared, optimized, and checked at different concentration ranges for ketamine ions. The results presented in this paper show that the adopted sensor developed has a wide concentration range (2.5×10^{-6} to 1.0×10^{-2} M), low limit of detection (8.5×10^{-7} M), good Nernstian slope (55.8 ± 0.3 mV/decade). Furthermore, this sensor showed good selectivity for ketamine in presence of some common excipients. In addition, this electrode produced reproducible results.

2. Experimental

2.1. Reagents

Ketamine (Ketamine hydrochloride) KTCl (Fig. 1); [2-(2-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride] [6740-88-1] (Chemical Formula $C_{13}H_{16}CINO \cdot HCl$, CAS: 6740-88-1, Molecular Weight = 274.19 g/mol), its pharmaceutical preparations (Ampoules 50 mg/mL), were provided by General Administration of Pharmacy, (Ministry of Health, Gaza-Palestine). Phosphotungstic acid (PTA), phosphomolybdic acid and sodium tetraphenylborate (Na-TPB) were obtained from Sigma. Dibutyl phthalate (DBP), dioctyl phthalate (DOP), dioctylsebacate (DOS), tris(2-ethylhexyl) phosphate (TEPh), poly vinyl chloride (PVC) of high relative molecular weight and tetrahydrofuran (THF) were obtained from Aldrich chemical company. All reagents used were chemically pure grade.
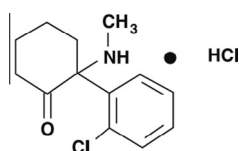

Fig. 1. The chemical structure of ketamine hydrochloride.

2.2. Apparatus

Potentiometric measurements were carried out with a digital millivoltmeter (SR-MUL-3800). pH measurements were made on a digital pH meter (Wissenschaftlich-Technische Werkstatten GmbH (WTW)-Germany) at room temperature ($25.0 \pm 1.0\,°C$). The performance of the electrode was investigated by measuring the emfs of KT solutions in a concentration range of 10^{-7} to 10^{-1} M by serial dilution. Each solution was stirred and the potential reading was recorded when it became stable, and plotted as a logarithmic function of KT cation activities

2.3. Preparation of the electroactive materials

Electroactive materials made from ketamine hydrochloride (KTCl) and one of the following substances: phosphotungstic acid (PTA), phosphomolybdic acid (PMA), or sodium tetraphenyl borate (Na-TPB) according to a previously reported method [9,13]. These electroactive materials were used as the active substances for preparing the electrodes of ketamine hydrochloride.

2.4. Preparation of silver-coated electrode

A pure silver rod of 1 mm diameter and 12 cm in length was insulated leaving 2 cm at one end for coating and 1 cm at the other end for connection. The coating solution was prepared by dissolving 1.0% KT-TPB, 48.2% PVC, and 50.8% TEPh in 5 ml THF. The polished surface of the silver rod was coated with active membrane by dipping the exposed end into the coating solution and allowing the film to dry in air for about 1 min. The process was repeated until a plastic film of approximately 1 mm thickness was formed (about 10 times). The prepared electrode was preconditioned by soaking for 10 min in 10^{-3} M KTCl solution.

2.5. Effect of interfering ions

Potentiometric selectivity factors of the electrode were evaluated by applying the matched potential method (MPM) and the separate solution method (SSM) [35]. According to the MPM, the activity of KT (I) was increased from $a_A = 1.0 \times 10^{-5}$ M (reference solution) to $\tilde{a}_A = 5.0 \times 10^{-5}$ M, and the change in potential (ΔE) corresponding to this increase were measured. Next, a solution of an interfering ion of concentration a_B in the range $1.0 \times 10^{-1} - 1.0 \times 10^{-2}$ M is added to new 1.0×10^{-5} M (reference solution) until the same potential change (ΔE) was recorded. The selectivity factor for each interferent was calculated using the Eq. (1):

$$K_{KT,J^{z+}}^{Pot} = \frac{a_{KT}}{a_j} \quad (1)$$

In the SSM [35], the potential of a cell comprising a working electrode and a reference electrode is measured in two separate solutions, one containing the ketamine ions, E_1, and the other containing the interferent ions (J), E_2, and S is the slope of the calibration graph. These values were used to calculate the selectivity coefficient from the following equation:

$$\log K_{Drug,J^{z+}}^{Pot} = \frac{E_2 - E_1}{S} + \log[Drug] - \log[J^{z+}]^{1/z} \quad (2)$$

2.6. Determination of KTCl in real sample

2.6.1. Potentiometric titration method

The potentiometric titration of different volumes of 1.0×10^{-3} M and 1.0×10^{-2} M KTCl solution: 5–10 ml of 1.0×10^{-2} M KTCl solution were transferred to a 25-ml beaker, and titrated with a standard