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Preparation of a cimetidine ion-selective electrode and its application to pharmaceutical analysis

Mojtaba Shamsipur [a,*], Fahimeh Jalali [a], Soheila Haghgoo [b]

[a] *Department of Chemistry, Razi University, Kermanshah, Iran*
[b] *Food and Drug Quality Control Laboratory, Ministry of Health and Medical Education, Tehran, Iran*

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Abstract

A novel cimetidine ion-selective electrode is prepared, characterized and used in pharmaceutical analysis. The electrode incorporates PVC-membrane with cimetidine–phospohotungstate ion pair complex. The electrode exhibits a Nernstian response for cimetidine in the concentration range 1.0×10^{-5}–1.0×10^{-2} M with a slope of 58 ± 1 mV per decade. The limit of detection is 5.0×10^{-6} M. The electrode displays a good selectivity for cimetidine with respect to a number of common foreign inorganic and organic species. It can be used in the pH range 3.0–5.5. The membrane sensor was successfully applied to the determination of cimetidine in its tablets as well as its recovery from a urine sample.

Keywords: Ion-selective electrode; Cimetidine; Analysis; Potentiometry

1. Introduction

Cimetidine (*N″*-cyano-*N*-methyl-*N′*[2-[(5-methyl-1H-imidazole-4-y1)methyl]thio]ethyl]-guanidine is a potent H_2-receptor antagonist which inhibits gastric acid secretion in humans and has been proven to be highly effective in the treatment of duodenal ulcer [1–4]. Due to the vital importance of the assay of cimetidine in pharmaceutical and in biological fluids, several analytical methods including chromatography [5–9], spectrophotometry [10–18] and titrimetry [19,20] have been reported for the determination of the drug in its pure and dosage forms. However, some of these methods need expensive equipment and/or are time-consuming.

In recent years, the potentiometric membrane sensors have been widely used in pharmaceutical analysis [21–23]. This is mainly due to simple design, low cost, adequate selectivity, low detection limit, high accuracy, wide concentration range and applicability of the selective electrodes to colored and turbid solutions. In 1987, a PVC-membrane electrode based on the salt of cimetidine with tetrakis(*m*-chlorophenyl)borate as ion-exchanger for the potentiometric determination of cimetidine was reported in the literature [24]. Besides several cation-and anion-selective

* Corresponding author. Tel.: +98-831-723-307; fax: +98-831-831-618.
E-mail address: shamsipur@razi.ac.ir (M. Shamsipur).

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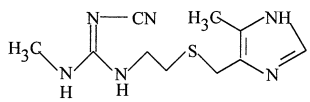
electrodes [25–31], we have recently reported two new membrane electrodes for the determination of ketoconazole [32] and clotrimazole [33] in their pure and pharmaceutical forms and also in biological fluids. In this work, we describe a simple potentiometric PVC-membrane sensor for the determination of cimetidine in pharmaceutical preparations. The membrane used in this electrode was made from liquid-plasticized PVC and was based on a water-insoluble cimetidine–phosphotungstate ion pair complex as an ion-exchanger.



Cimetidine

2. Experimental

2.1. Reagents

All chemicals used in this study were of the highest purity available and used without any further purification except for vacuum drying over P_2O_5. Doubly distilled deionized water was used throughout. Reagent grade cimetidine hydrochloride and its tablets were obtained from Iran Daru (Tehran, Iran). Reagent grade dibutyl phthalate (DBP), tetrahydrofuran (THF), phosphotungstic acid, sodium tetraphenylborate (Na TPB), high relative molecular weight PVC and the chloride salts of all cations used, (all from Merck) were used as received.

A stock standard solution of 0.05 M cimetidine hydrochloride was prepared by dissolving 0.1444 g of pure drug in 10 ml water (pH 3.5). A 0.1 M HCl solution was used for the pH adjustments. The working solutions were prepared by appropriate dilution of the stock solution with water while keeping pH constant at a value of 3.5.

2.2. Preparation of the electrode

Powdered PVC (29 mg), phosphotungstic acid (2 mg) and plasticizer-mediator DBP (69 mg) were thoroughly dissolved in 5 ml of THF. The resulting mixture was transferred into a glass dish of 2 cm diameter and the solvent was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube of 3–5 mm internal diameter in top was dipped into the mixture for about 10 s, so that a membrane of about 0.3 mm thickness was formed. The tube was pulled out from the mixture and kept at room temperature for about 1 h. The tube was then filled with the internal filling solution (0.01 M cimetidine). The electrode was finally conditioned for 1 h by soaking in a 0.05 M cimetidine. A silver/silver chloride electrode was used as a reference electrode.

2.3. Emf measurements

All emf measurements were carried out with the following assembly, Ag–AgCl, 0.01 M KCl/internal solution (0.01 M cimetidine)/PVC membrane/test solution/Ag–AgCl, 3 M KCl.

A model 692 Metrohm ion analyzer pH/mV meter was used for the potential measurements at 25.0 ± 0.1 °C. Single junction Ag–AgCl reference electrodes from Azar Electrode Company (Orumieh, Iran) were used. All measurements were carried out in a 50 ml double-walled glass cell, with constant magnetic stirring of the test solution.

2.4. Procedures

2.4.1. Tablets

A homogenized powder was prepared from ten accurately weighed cimetidine tablets. An appropriate amount of this powder (0.1970 g) was transferred into a 100 ml Erlenmeyer flask. Dissolution of the drug was assisted by means of a magnetic stirrer and by addition of a few drops of HCl 1.0 M. The mixture was then filtered and made up to the mark with water in a 500 ml volumetric flask while keeping the pH constant at 3.5. The cimetidine content was determined by the proposed ion-selective electrode, using the calibration method.

2.4.2. Recovery of cimetidine from urine samples

A 2.5 ml portion of 0.01 M cimetidine solution was transferred into a 25 ml volumetric flask. Then 2.0 ml of the urine sample and 8 ml water was added and the pH of the solution was adjusted to 3.5 by HCl (0.1 M). The cimetidine content of the solution was determined by calibration method using the proposed sensor as an indicator electrode.

3. Results and discussion

3.1. Membrane material

Cimetidine hydrochloride and other organic amines are well known for reacting with phosphotungstic acid or phosphomoybdic acid to form stable ion-pair complexes [34]. In this work, the ion-pair complex of cimetidine with phosphotungstic acid was obtained in situ by soaking the PVC membranes in a 5×10^{-2} M cimetidine hydrochloride solution for 1 h. Among different solvent mediators tested, DBP exhibited a proper behavior regarding a fast response time and good reproducibility of the emf values of electrodes. The optimal membrane composition obtained was a PVC:DBP:phosphotungstic acid ratio of 29:69:2%. The resulting calibration graph then showed a Nernstian emf-log[cimetidine] slope over a relatively wide concentration range.

The influence of the concentration of internal solution on the potential response of the cimetidine-selective sensor was studied. The cimetidine concentration was changed from 1.0×10^{-4} to 5.0×10^{-2} M and the emf versus log[cimetidine] plots were obtained. It was found that the variation of the concentration of the internal solution does not cause any significant difference in the potential response, except for an expected change in the intercept of the resulting plots. A 1.0×10^{-2} M concentration of the reference solution (at pH 3.5) is quite appropriate for smooth functioning of the electrode system.

The optimum conditioning time for the membrane sensor in a 5.0×10^{-2} M cimetidine (at pH 3.5) is 1 h. It then generates stable potentials when placed in contact with cimetidine solutions. The electrodes were rinsed with water and stored in air between measurements.

The average time required for the cimetidine-selective electrode to reach a potential within $\pm$ 1 mV of the final equilibrium value after successive immersion of a series of cimetidine solutions, each having a 10-fold difference in concentrations, was measured. Stable responses were achieved within 5–15 s for cimetidine concentrations of 10^{-2}–10^{-5} M. The electrode exhibited a day-to-day reproducibility of about $\pm$ 0.5 mV for at least 2 weeks after preparation, while stored in water.

The emf response of the proposed cimetidine membrane sensor (prepared under optimal membrane ingredients) indicates a rectilinear range from 1.0×10^{-5} to 1.0×10^{-2} M (Fig. 1). The slopes of the calibration curves were 58 ± 1 mV per decade. The limit of detection, as determined from the intersection of the two extrapolated segments of the calibration graph was 5×10^{-6} M.

In order to study the pH-dependence of the electrode potential, the graph of emf versus pH was constructed. The pH of the initial solutions was changed by the addition of very small volumes of 1.0 M sodium hydroxide solution. Fig. 2 shows a typical profile for a 3.0×10^{-3} M cimetidine concentration. As seen, the potential is rather independent of pH in the range 3.0–5.5 (the pK_a value of cimetidine is 6.8). However, at very high acidic solution, an anionic response is observed which is due to Donnan failure. Above pH 6, the potential response decreases drastically because of the decreasing concentration of the cationic form of cimetidine.

The extent of interference of various common cationic species was studied by the fixed interference method [35,36]. The potentiometric selectivity coefficients were evaluated graphically using the expression $\log K^{pot} = \log (a_k)/(a_i)^{1/z}$, where a_k

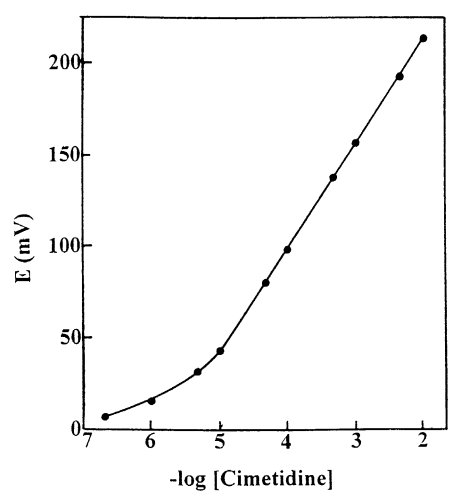


Fig. 1. Calibration graph for the cimetidine ion-selective electrode.

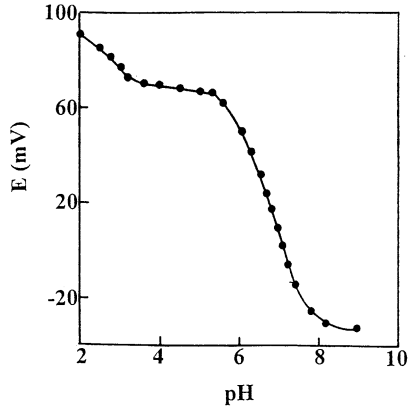


Fig. 2. Effect of pH of test solution on the potential response of the cimetidine ion-selective electrode.

is the activity of cimetidine and a_i that of interfering ion, and z is the charge of interfering ion. The resulting selectivity coefficients are summarized in Table 1. The interference from K^+ becomes a problem when using a 3 M KCl solution in the Ag/AgCl inner reference electrode. For this reason, a 0.01 M KCl solution was used as the internal solution of the inner Ag/AgCl reference electrode. Common excipients used in pharmaceutical preparations, like sugar, starch, etc. did not interfere.

A comparison between the proposed cimetidine-selective electrode and that reported in the literature [24], revealed some superiorities in terms of the easier ion-exchanger preparation (in situ preparation) and improved linear range (1.0×10^{-5}–1.0×10^{-2} vs. 2.0×10^{-5}–1.0×10^{-2} M), detection limit (5.0×10^{-6} vs. 2.0×10^{-5} M) and sensitivity (a slope of 58.0 vs. 50.7 mV per decade).

Table 1
Potentiometric selectivity coefficients of the cimetidine electrode

Interference	K^{pot}	Interference	K^{pot}
Glycine	1.0×10^{-3}	Mg^{2+}	1.0×10^{-4}
L-Histidine	1.0×10^{-3}	Ca^{2+}	1.0×10^{-4}
L-Lysine	6.32×10^{-4}	NH_4^+	1.42×10^{-2}
Glucose	1.0×10^{-3}	K^+	3.3×10^{-2}
Urea	1.0×10^{-3}	Na^+	1.78×10^{-2}

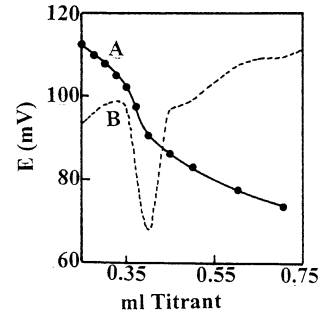


Fig. 3. Potentiometric titration curve (A) and its first derivative (B) of 20.0 ml of 1.0×10^{-3} M cimetidine at pH 3.5 with 0.05 M NaTPB using the proposed sensor as an indicator electrode.

The proposed sensor was used as an indicator electrode in potentiometric titration of 20.0 ml of 1.0×10^{-3} M cimetidine (at pH 3.5) with 0.05 M NaTPB. Fig. 3 shows the resulting titration curve and its first derivative. The recovery obtained from three replicate measurements was 100.5%.

The proposed membrane sensor proved to be useful for the assay of cimetidine content of pharmaceutical preparations by using direct reading of potential. A cimetidine tablet with a declared cimetidine content of 200 mg was analyzed by the proposed electrode. The results obtained from three replicate measurements was found to be 199 ± 1 mg cimetidine per tablet which is in satisfactory agreement with the declared amount. This is indicative of noninterference of the other ingredients and the excipients that are present in the formulations.

In order to investigate the applicability of the proposed cimetidine membrane sensor to the determination of the drug in the biological fluids, it was applied to the recovery of 7.22 mg cimetidine from a 2.0 ml urine sample. The percent recovery obtained from three replicate measurements was found to be 115.0 ± 5.0.

Inclusion compounds in which the host can admit a guest compound into its cavity without any covalent compounds being formed have been used extensively in fundamental studies, and have also found a wide variety of applications. Cyclodextrins are known to form several inclusion compounds with substrates and, indeed, are also known to inhibit side effects in drugs [37].

Thus, the proposed electrode was also used to evaluate the equilibrium constant of the β-cyclodextrin–cimetidine inclusion complex:

Cimetidine

$$+\beta\text{-Cyclodextrin} \overset{K_s}{=} \text{Inclusion Compound} \qquad (1)$$

Fig. 4 shows the emf response of the cimetidine-selective electrode in the absence and presence of β-cyclodextrin at pH 3.5. It should be noted that, after each titration of the cyclohextrin solutions, an experiment was performed in the absence of cyclodextrins to confirm the reproducible response of the proposed ion-selective electrode. The data were analyzed by assuming that the equilibrium (1) between cimetidine and β-cyclodextrin involves a 1:1 complexation. In this case, the equilibrium concentration constant, K_s, can be evaluated from the emf data by using the classical Hildebrand equation in the form [38]:

$$\frac{1}{v} = \frac{1}{K_s m_1} + 1 \qquad (2)$$

where v is the concentration of cimetidine complex with cyclodextrin over its total concentration and m_1 is the drug monomer concentration. The plot of $1/v$ versus $1/m_1$ for the data involving cimetidine binding to β-cyclodextrin is shown in Fig. 5. The linearity of the plot confirms the 1:1 stoichiometry of the resulting complex. The binding constant obtained for the complex is 137 ± 5.

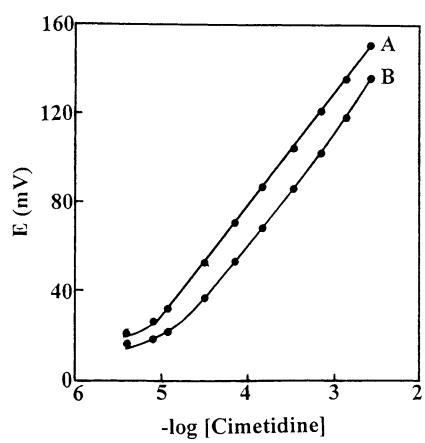


Fig. 4. Emf response of the cimetidine ion-selective electrode without (A) and with 0.01 M β-cyclodextrin (B).

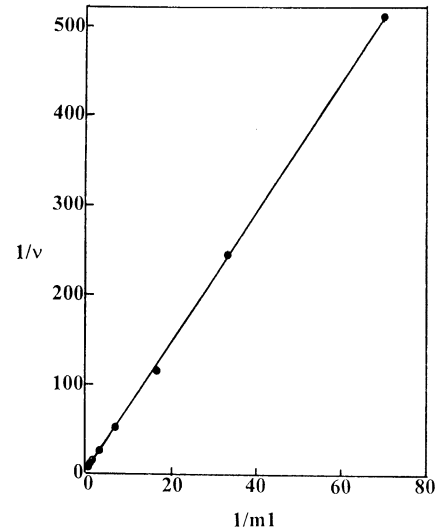


Fig. 5. Plot of $1/v$ versus $1/m_1$ for cimetidine binding to β-cyclodextrin.

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