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Preparation of a ticlopidine potentiometric sensor and its application to pharmaceutical and biological analysis

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ABSTRACT

Ticlopidine (Tic) ion selective liquid membrane electrode was constructed from poly (vinyl chloride) containing Tic-tetraphenylborate (Tic-TPB) as the sensing element in the presence of dioctylphthalate (DOP) as the plasticizing solvent mediator. The electrode shows nearly Nernstian response for the drug over the concentration range of 1.0×10^{-2}–5.0×10^{-5} M with cationic slope of 58.23 mV per concentration decade, and the response time is very short (≤10 s). The electrode potential is nearly stable over the pH range 3.8–5.4. The electrode exhibits good selectivity for the Tic with respect to a large number of inorganic ions, amino acids and some pharmaceutical substances. The sensor successfully was used for the determination of Tic in pharmaceutical and biological samples. The average recovery and RSD for the analysis of Tic in pharmaceutical and biological samples using the proposed method obtained 101.04, 98.90% and 1.14, 1.39%, respectively. The results are in good agreement with those obtained by voltammetry method.

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1. Introduction

Ticlopidine (Tic), 4-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydro-thieno-[3,2-c]pyridine (Scheme 1) is a potent and long acting thieno-[3,2-c]-pyridine derivative antithrombotic agent [1]. Tic is therapeutically used in the treatment of acute arterial thrombosis and in the prevention of stroke and myocardial infarct in high risk patients [2]. Although Tic is found to be superior to aspirin, has a different spectrum of side effects [3].

A limited number of analytical techniques have been used for the determination of Tic in pharmaceutical and biological samples. Several analytical methods included high performance liquid chromatography (HPLC) [4–11], reversed phase HPLC [12], gas chromatography (GC) [13–15], GC–MS [16], capillary electrophoresis [17] and Raman spectroscopy [18] have been reported for the determination of Tic in the literature. The proposed method in the European Pharmacopeia [19] is also a gas chromatographic method with flame-ionization detection. A flow injection analysis [20] using UV-detection is also reported. The voltammetric behavior of ticlopidine-HCl was studied using square- wave, sampled direct current and cyclic voltammetry [21]. In most cases analytical techniques used in the pharmaceutical analysis are sensitive, precise and selective, but quite expensive and complicated (for instance, the sample preparation is usually very time-consuming). That is why continuous investigations are being carried out in order to find cheaper, simpler and fast techniques that would also be precise and selective at the same time [22].

Although ion-selective electrodes (ISEs) have found many successful applications in pharmaceutical analysis [23] mainly because of their low cost, ease of use and maintenance and the simplicity and speed of the assay procedures [24], it has not been applied yet to the determination of ticlopidine. In this paper, we report a simple potentiometric PVC-membrane sensor for the determination of ticlopidine in pharmaceutical preparations and blood serum samples.

The membrane electrodes proposed in this study were made from plasticized-PVC using a water-insoluble ion-pair complex, ticlopidine-TPB, as ion-exchanger. The high lipophilicity and remarkable stability of this complex suggested its selective use as electroactive material in PVC matrix membrane sensors for the determination of ticlopidine. Moreover, it offers highly sensitive, selective and a convenient technique for the determination of ticlopidine hydrochloride in its pharmaceutical preparations and blood serum samples.

2. Experimental

2.1. Reagents and materials

All chemicals were purchased from Merck and were used of analytical reagent grade. Double distilled and deionized water was used throughout the experiments. Ticlopidine hydrochloride was obtained from Fluka (Buchs, Switzerland).

Aqueous 1.0×10^{-3}–5.0×10^{-5} M of the drug solution was prepared by accurate dilutions of a standard 1.0×10^{-2} M stock drug solution. Solutions were stable for at least 2 weeks if stored in a cool and dark

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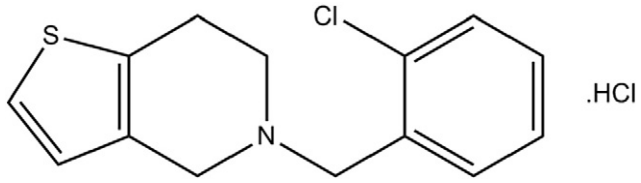

Scheme 1. Chemical structure of Ticlopidine HCl.

place. Ticlopidine tablets were purchased from Arya Pharmaceutical Co., Tehran-Iran, and Amin Pharmaceutical Co., Isfahan-Iran.

Poly(vinyl chloride) (PVC) of high molecular mass was from Aldrich, sodium tetraphenylborate (NaTPB), tetrahydrofuran (THF) solvent and dioctylphthalate (DOP) plasticizer were obtained from Merck, dibutylphtalate (DBP) plasticizer was purchased from Daejung, South Korea.

2.2. Procedures

2.2.1. Preparation of Tic-TPB ion-pair

For an ISE to be selective with respect to a single type of ions, its membrane should contain a substance that can reversibly bind the ion under determination and at the same time exhibit the minimum solubility in aqueous solutions. Substances with such properties are called electroactive compounds (EAC) [25]. Tetraphenylborate and its derivatives are used most extensively in EAC for cation-selective electrodes [26]. Ticlopidine hydrochloride ($pK_a = 7.64$) [27] behaves as cation in acidic medium. This fact suggests the use of anionic type of ion exchanger, sodium tetraphenylborate. Ticlopidine tetraphenylborate (Tic-TPB) was prepared by mixing 50 ml of 1.0×10^{-2} M of aqueous drug solution; with 50 ml of 1.0×10^{-2} M of aqueous solution of NaTPB till precipitation occurs. The resulting precipitate was left in contact with its mother liquor overnight to assure complete coagulation. The precipitate was then filtered, washed with cold distilled water, dried at room temperature for 24 h and ground to a fine powder, forming the ion-pair complex. The dried ground ion-pair has a melting point of 156 °C. Elemental analysis was carried out to study the formation of the complex. Stoichiometry of the ion-pair was 1:1 as confirmed by elemental analysis using automatic CHN analyzer (Flash EA 1112 Eager). The C, H and N percentages were 78.21, 6.35 and 1.91%, respectively. The corresponding calculated ones are 77.61, 6.68 and 2.38%, respectively. The result of the elemental analysis agrees positively with molar ratio 1:1 of the reacting substances.

2.2.2. Electrode preparation

Different percentages of Tic-TPB were used to obtain 2, 4, and 6% in the membrane. The membrane was prepared by dissolving the required amount of PVC in 3 ml THF. The calculated amount of ion-pair was dissolved in THF and mixed with the PVC solution, and then the calculated volume of a solution of plasticizer was added. The resulting mixture was transferred into a glass dish of 2 cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube (3–5 mm o.d.) was dipped into the mixture for about 5 s, so that a transparent membrane of about 0.3 mm thickness was formed. The tube was then pulled out from the mixture and kept at the room temperature for about 24 h [28–35]. The tube was then filled with an internal filling solution (1.0×10^{-3} M of ticlopidine hydrochloride). The electrode was finally conditioned by soaking in a 1.0×10^{-3} M drug solution for 24 h. An Ag/AgCl electrode was used as an internal reference electrode.

2.2.3. Emf measurements

All emf measurements were carried out with the following cell assembly: Ag–AgCl, KCl (3 M)/internal solution 1.0×10^{-3} M ticlopidine HCl/PVC membrane/test solution/Ag–AgCl, KCl (3 M). A HIOKI Digital Multi Meter (model 3256–50) was used for potential measurements at 25 ± 1 °C.

Table 1
Composition of the different Tic-TPB representative membranes and slopes of the corresponding calibration graphs.

Composition % w/w			Slope (mV/decade) ± SD[a]	Linear concentration range (mol/L)	Detection limit (mol/L)
Ion-pair	Plasticizer	PVC			
2	66 (DOP)	32	55.56 ± 1.25	10^{-2}-5×10^{-5}	1.04×10^{-5}
4	64	32	56.23 ± 1.55	10^{-2}-5×10^{-5}	1.15×10^{-5}
6[b]	**62**	**32**	**58.23 ± 1.08**	**10^{-2}-5×10^{-5}**	**1.12×10^{-5}**
2	66 (DBP)	32	56.84 ± 1.71	10^{-2}-5×10^{-5}	1.00×10^{-5}
3	65	32	55.13 ± 1.19	10^{-2}-5×10^{-5}	1.38×10^{-5}

[a] Standard deviation (at least 6 determinations).
[b] Optimum composition.

The electrode and the double junction Ag/AgCl reference electrode were immersed in aqueous drug solutions in the range of 1.0×10^{-2}–1.0×10^{-6} M. 10 ml aliquots of 1.0×10^{-2}–1.0×10^{-6} M standard solution of ticlopidine HCl were transferred into a 50 ml beaker and the membrane electrode in conjunction with Ag/AgCl reference electrode were immersed in the solution. The measured potential was plotted against the logarithm of drug concentration. The electrode was washed with distilled water blotted with tissue paper between measurements.

2.3. Samples preparation

2.3.1. Tablets

Ticlopidine HCl tablets (250 mg/tablet) were accurately weighed, powdered and the average weight of one tablet was calculated. A quantity of the powder was transferred to a 50 ml volumetric flask and filled to the mark with distilled water to prepare a 10^{-2} M aqueous solution of ticlopidine HCl. The ticlopidine HCl content was determined by both the standard addition method and potentiometric titration of the solution with a standard sodium tetraphenylborate (NaTPB) solution (0.010 M) using the proposed method.

2.3.2. Blood serum samples

Different amounts of ticlopidine (3–15 mg) and 2.5 ml serum of a healthy person were transferred to 10 ml volumetric flask and the pH of the solutions were adjusted to 4.0 (the optimum pH range of the electrode performance) by HNO_3 (0.01 M). The solutions were diluted to 10 ml with distilled water and subjected to potentiometric analysis using the proposed electrode.

3. Results and discussion

3.1. Effect of composition

The membrane composition was varied to obtain the best performance characteristics, (slope of calibration graph, rectilinear concentration range, detection limit, and reproducibility of the results). The potentiometric response of the electrodes prepared with the optimum

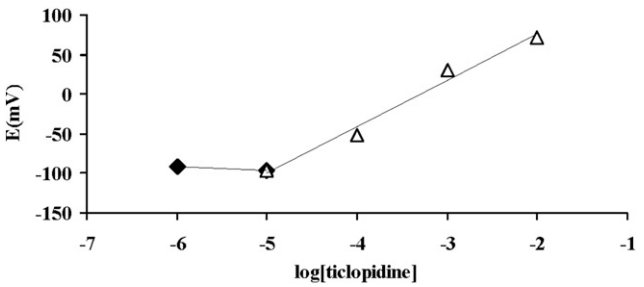

Fig. 1. The calibration curve of the proposed ticlopidine ion selective electrode.

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