

# Comparative study of three polymeric membrane electrodes selective to tizanidine<sup>1</sup>

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## Abstract

Three types of polymeric electrodes were elaborated using a poly(vinyl chloride) film plasticized with a dioctyl phthalate–nitrobenzene mixture and containing an ion pair of the drug tizanidine. The membrane of the so-called conventional electrode, which includes an internal Ag/AgCl reference, was immobilized on a micropipette tip. A single-layer electrode was prepared by coating a graphite rod with the membrane, while the graphite rod of a two-layer electrode was previously coated with a poly(4,4'-biphenol) film before the sensitive membrane was deposited. These electrodes exhibit a Nernstian response in the concentration range  $5 \times 10^{-6}$ – $1 \times 10^{-2}$  M with a slope between 55 and 57 mV per decade. The response is not affected by pH between 3 and 7. The influence of several parameters involved in the construction of these electrodes on their lifetime is discussed, the highest durability being observed for the conventional electrode. Selectivity coefficients against various organic and inorganic cations were evaluated. The conventional electrode was applied to the determination of tizanidine in drug formulations using direct potentiometry.

*Keywords* Potentiometry, Pharmaceuticals, Polymeric membrane electrodes, Tizanidine

The development of simple, cheap and easy to construct and use electrodes is of considerable interest in pharmaceutical analysis and the modifications to the technology of selective electrodes to increase their performance are being intensively investigated [1–3].

Easier manipulation of liquid membrane electrodes was introduced in the 1970s with two types of polymeric sensors. The first, developed by Moody et al [4], is called a conventional electrode and includes an internal reference element which consists of a silver/silver chloride wire dipped in a potassium chloride solution in contact with the polymeric sensing membrane. This ensures a stable internal reference potential.

The second kind of electrode uses an internal solid contact (ISCE) [5]. The membrane is directly immobilized on a platinum surface [6] or on a graphite rod [7]. Despite several advantages which make these ISCEs very popular [8,9], the absence of a reversible redox couple as internal reference may lead to some problems related to the transduction of an ionic conduction in the membrane to an electrical conduction in the support [8]. As the generation of a potential at the support–membrane interface results from such a redox couple, which can be an impurity in the poly(vinyl chloride) (PVC) membrane, large differences in potential can be expected between different sensors of the same type and also for a given electrode as a function of time [10,11].

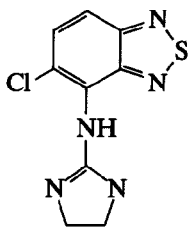
To overcome this situation, several workers have recommended inserting an additional layer acting as a reversible redox couple between the

<sup>1</sup> This paper is dedicated to the memory of the late Professor G J Patriarche

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sensing membrane and the conducting support, providing the so-called two-layer electrode. Such devices already studied include PbS/Ag<sub>2</sub>S/Ag, LaF<sub>3</sub>/AgF/AgCl/Ag, PVC-valinomycin/quinone-hydroquinone/graphite [8] and PVC-valinomycin/potassium tetrphenylborate/silver tetrphenylborate/Ag [12] systems. Glass electrodes have also been used as internal references for ISCEs [13], and further, more recently, a two-layer electrode whose internal reference is made of poly(1-pyrenamine) deposited by electrooxidation on a graphite rod [14].

Despite the frequent use of ISCEs, discussion about the precise function of the internal contact remains open [8]. The aim of this work was to compare the characteristics of three electrodes selective to tizanidine: a conventional, a single-layer and a two-layer electrode.



Tizanidine [5-chloro-4-(2-imidazolyl-2-amino)-2,1,3-benzothiadiazole], with the structure shown, is a central nervous system relaxant [15–18] whose principal mode of action is located in the spinal column [17].

## EXPERIMENTAL

### Reagents

Tizanidine hydrochloride was kindly provided by Sandoz (Brussels). 4,4'-Biphenol was purchased from Aldrich and PVC of high molecular weight from Janssen. Other reagents and solvents (Merck) were of analytical-reagent grade. Solutions were prepared using deionized water. Standard solutions were prepared by successive dilutions of a 0.1 M stock solution.

### Preparation of the membrane

The ion pair was prepared by mixing equal

volumes of 0.01 M solutions of tizanidine hydrochloride and of the counter ion. Three different precipitating agents were submitted to analysis: phosphotungstic and silicotungstic acids and sodium tetrphenylborate. The precipitate obtained was filtered in a sintered-glass crucible (G4), washed with deionized water and dried at 50°C.

The membrane was prepared by dissolving PVC in cyclohexanone (0.32 g in 4 ml) with stirring in a water-bath at 50°C. A 1-ml volume of dioctyl phthalate, 1 ml of nitrobenzene and 0.02 g of the ion pair were successively added; this last amount corresponds to a  $1 \times 10^{-3}$  M concentration of the active material in the membrane. This mixture was sonicated to ensure homogeneity.

### Assembly of the electrode

**Conventional electrode** This model was prepared by dipping a micropipette tip (polypropylene, id 2 mm) in the above polymer solution (thickness of the membrane ca. 2 mm). The tip was dried at room temperature for 1 h and then filled with a solution containing 0.1 M potassium chloride and 0.01 M tizanidine hydrochloride. A silver wire coated with silver chloride was used as internal reference.

**Single-layer electrode** A pyrolytic graphite rod (spectrographic quality, diameter 2 mm, Ultra Carbon, Bay City, MI), shaped as a pencil, was polished with a smooth abrasive paper (Waterproof, P600), washed and dried. The rod was dipped in the polymer solution for 30 min in order to ensure good adhesion of the polymer film. It was dried at room temperature for 1 h.

**Two-layer electrode** A similar graphite rod was first modified with a poly(4,4'-biphenol) layer. Electropolymerization was performed for 1 min by anodic oxidation [19] at +950 mV vs SCE from a  $5 \times 10^{-3}$  M 4,4'-biphenol monomer solution in acetonitrile containing 0.1 M sodium perchlorate. The modified graphite rod was briefly dipped in the polymer solution and dried. This last cycle was repeated three times in order to ensure a sufficient thickness of the sensing membrane. The immersion time in the polymer solution must be short because poly(4,4'-biphenol) is slowly dissolved by cyclohexanone.

### Potentiometric measurements

Measurements were made using a Tacussel Minisis 6000 millivoltmeter and a Tacussel Iono-processor II, a millivoltmeter which is able to convert potential responses into concentration or slope units. Potentials are referred to the saturated calomel electrode (SCE). All measurements were made using a 0.1 M acetate-acetic acid buffer (pH 4.6). Aliquots of 0.1 ml of standard solutions ranging from  $1 \times 10^{-6}$  to 0.1 M were added to 10 ml of the buffer with stirring to establish calibration graphs between  $1 \times 10^{-8}$  and  $1 \times 10^{-3}$  M, 1.1 ml of 0.1 M standard solution was added to give a concentration of 0.01 M in the cell. Potentials, considered for a drift lower than 0.1 mV per 10 s, were plotted against the logarithm of tizanidine concentration.

When not in use, the electrode was stored in a 0.01 M tizanidine solution in order to regenerate the membrane. This procedure increases the lifetime of the electrode.

## RESULTS AND DISCUSSION

### Structural properties and behaviour of the electrodes

The influence of the precipitating agent utilized to prepare the ion pair of tizanidine was first investigated. The results obtained with the conventional electrode are summarized in Table 1. They show that silicotungstic acid improves both the linearity and the detection limit. This tendency also appears when using the single- and two-layer electrodes. This precipitating agent was selected for further investigations.

TABLE 1

Influence of the nature of the precipitating agent utilized to prepare the ion pair on the characteristics of the conventional electrode

Parameter	Precipitating agent		
	Sodium tetraphenylborate	Phosphotungstic acid	Silicotungstic acid
Slope (mV per decade)	53	55	57
Linearity range (M)	$1 \times 10^{-2} - 1 \times 10^{-5}$	$1 \times 10^{-2} - 3.5 \times 10^{-6}$	$1 \times 10^{-2} - 3.9 \times 10^{-6}$
Detection limit (M)	$6.3 \times 10^{-6}$	$3.2 \times 10^{-6}$	$2.5 \times 10^{-6}$
Correlation coefficient	0.9980	0.9996	0.9997

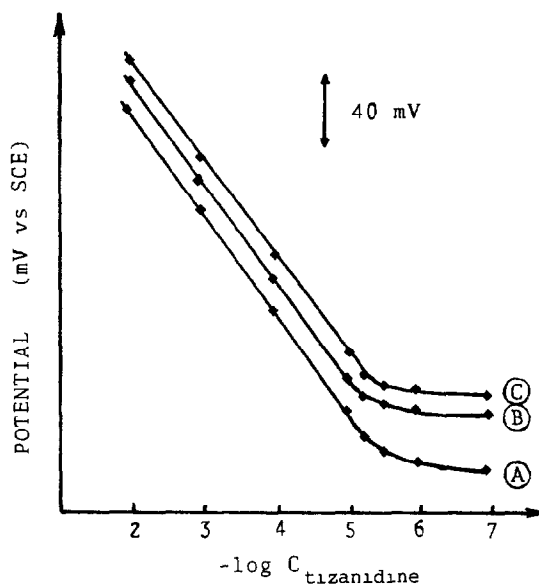


Fig 1 Calibration graphs for the three electrodes selective to tizanidine. 0.1 M acetate buffer, pH 4.6 (A) Conventional electrode, (B) single-layer electrode, (C) two-layer electrode. Equations: (A)  $y = -57x + 240$ , (B)  $y = -56x + 356$ , (C)  $y = -56x + 568$ .

Platinum has frequently been used to construct ISCEs but other conducting supports such as silver, lead, copper, graphite [7,8] or a conductive epoxy resin [11] have also been proposed. Graphite was selected as the redox behaviour of poly(4,4'-biphenol) on this material and its electropolymerization conditions are well documented [19].

The calibration graphs obtained with each electrode are shown in Fig 1. These curves are very similar provided that the electrodes are freshly prepared. This agrees very well with previ-

ous results obtained from a comparison of different procedures for the construction of polymeric membrane electrodes [11,14,20] However, the response of each electrode will evolve differently with time

The lifetime of the electrodes was evaluated from the variation of the slope of the calibration graph. Considering that the electrode remains usable when its slope is not less than 52 mV per decade, it appears from Fig 2 that the conventional electrode exhibits a lifetime of 4 months whereas the two-layer electrode is stable for 2 months and the single-layer electrode for 1 month. Similar conclusions can be deduced from the change in the lower limit of the linear response as a function of time (Fig 3). Each electrode concerned with this study was utilized at a frequency of two measurements per day. This parameter has a marked influence on the lifetime of the electrode and a conventional electrode stored without use for 6 months in a solution of tizandine remains operational. The higher durability of the conventional electrode also appears from the evolution of its potential with time, but care must be taken when using this parameter for the evaluation of the electrode lifetime. With freshly prepared electrodes, a drift in potential is also observed but the electrode is considered to be

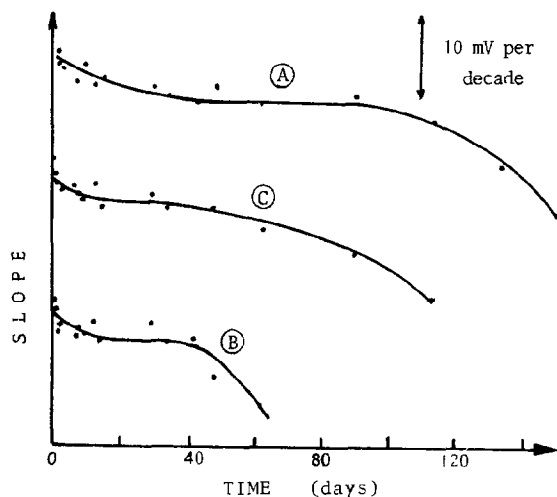


Fig 2 Change of the slope of the calibration graphs as a function of time (A) Conventional electrode, (B) single-layer electrode, (C) two-layer electrode

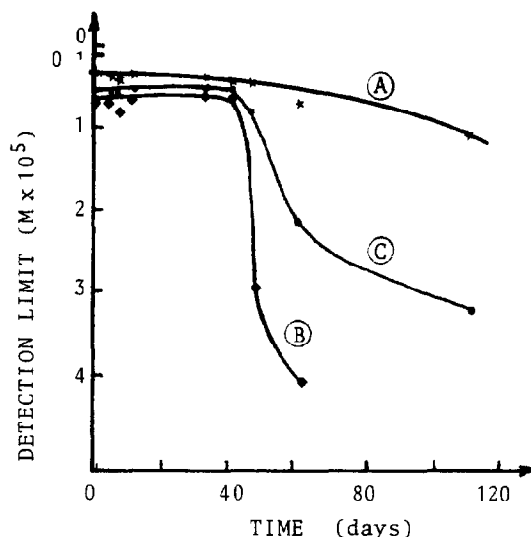


Fig 3 Change of the lower limit of the linear response as a function of time (A) Conventional electrode, (B) single-layer electrode, (C) two-layer electrode

operational as its calibration graphs, if they are not superimposed, exhibit identical slopes

The lifetime of the electrode, which mainly depends on the lipophilicity of the ion pair and of the plasticizers, is often limited by the diffusion of these species from the membrane to the aqueous solution [10,21–23]. The amount of these components lost differs from one electrode to another, depending on its conception. The present electrodes, including the conventional type, exhibit shorter lifetimes than the ISCEs of Lima and Machado [11] and Moody et al [24], which are characterized by a more uniform thickness. This difference can be understood by the fact that the activity of the sensor is localized in the superficial layer of the membrane in contact with the solution to be analysed [10]. To correlate the lifetime with the membrane thickness, the internal layers of the membrane must supply the depleted superficial layer with the ion pair and the plasticizers. The limited lifetime of the present ISCEs is attributed to a loss of the plasticizers, the thin film of the single- and two-layer electrodes being more rapidly altered than the membrane of the conventional electrode which is protected by the micropipette tip. Moreover, the loss of the ion pair at the external interface of the

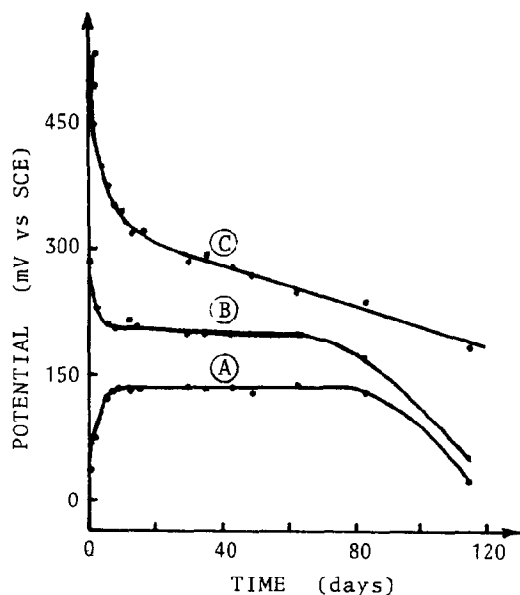


Fig. 4 Drift of the recorded potential as a function of time. Tizanidine concentration  $1 \times 10^{-3}$  M. (A) Conventional electrode, (B) single-layer electrode, (C) two-layer electrode.

conventional electrode is compensated for by that provided from the bulk of the membrane.

The lifetime of the two-layer electrode, which is better than that of the single-layer electrode, is probably related to the stronger adherence of the sensing membrane, which is fixed in the former instance on another film, the poly(4,4'-biphenol) deposited on the support by electropolymerization.

Considering the drift of the potential with time (Fig. 4), each electrode is characterized by a first period during which the potential is shifted by more than 100 mV. This can be related to three major phenomena common to the three electrodes: diffusion of the ion pair and of the plasticizers from the membrane [10,22] and conversely water absorption by the membrane [25,26] and its contamination by interfering ions [22] present in the sample. These phenomena may modify several properties of the membrane, such as composition, conductivity [22,27,28] and extraction coefficients [29].

In addition to the above-mentioned modifications and considering the single-layer electrode,

the stability of the potential at the graphite-membrane interface is not ensured by a real internal reference. Hulanicki and Trojanowicz [30] suggested that this interface potential, and also that of the platinum-membrane assembly to a greater extent [26,30,31], results from the  $O_2$ - $H_2O$  reversible redox system [8,11,25,30-32]. Hence the potential drift observed during the first period of use corresponds to the penetration of water and oxygen through the membrane to install an internal reference at the interface [8,11,25]. Other reversible redox couples such as quinone-hydroquinone can be involved by using pyrolytic graphite as conducting support [33-36], especially when the surface is previously polished, creating an overheating which favours its slow oxidation in the presence of air [33,34].

The coverage of graphite with a poly(4,4'-biphenol) layer did not allow the potential to be stabilized as these variations are double that observed for the single-layer electrode. In addition, the electrochemical oxidation of the graphite surface resulting from the electropolymerization process may lead to the formation of additional functional groups. Moreover, as these redox reactions involve proton transfers in the water film absorbed through the PVC membrane [37], the potentials of these couples are pH dependent.

The slow drift of the potential recorded after the stabilization period with the two-layer electrode (1.2 mV per day) (Fig. 4C) is related to the degradation of the poly(4,4'-biphenol) film. This process results from the presence of the plasticizers, as a graphite rod covered with only this film loses it after 1 week by dipping in nitrobenzene. Both the conventional and the single-layer electrodes, devoid of the poly(4,4'-biphenol) film, exhibit good reproducibility after the stabilization period (Fig. 4A and B).

Similar response times were observed for each electrode, ranging from 15 s for concentrations above  $1 \times 10^{-4}$  M to 2 min for lower concentrations.

#### *Effect of pH*

The influence of pH was established by plotting the potential of each electrode as a function of this parameter for tizanidine concentrations of

$1 \times 10^{-3}$  and  $1 \times 10^{-4}$  M Curves A and B in Fig 5 are related to the two-layer electrode but the single layer and the conventional electrodes exhibit similar behaviour The decrease in the potential above pH 7 is attributed to a decrease in the protonated form of tizanidine ( $pK = 7.46$ ) according to an acid-base equilibrium The independence of the electrode response between pH 3 and 7 is evidence for the full coverage of the poly(4,4'-biphenol) layer by the PVC membrane as the uncovered poly(4,4'-biphenol) film exhibits a linear decrease in potential with increasing pH, the slope being 37 mV per pH (Fig 5D) Electropolymerizations of 1-pyrenamine [14], 1,2-diaminobenzene and phenol [38] on a graphite support give similar results The response of the poly(4,4'-biphenol) electrode cannot be merely related to the 4,4'-biphenylquinone-4,4'-biphenol redox potential, for which a slope of 59 mV would be expected [19,39], but to the graphite rod itself [38,40], as shown in Fig 5C The improvement in the response brought about by the

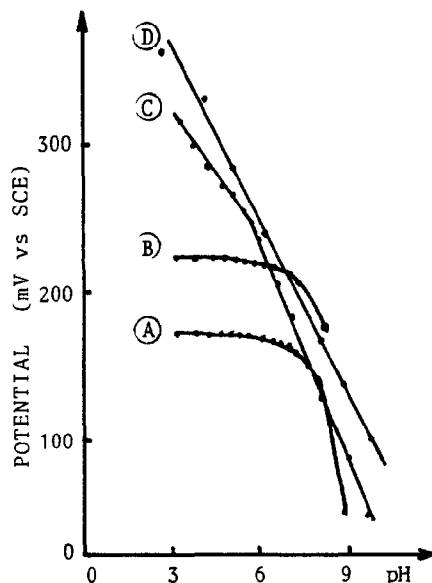


Fig 5 Drift of the recorded potential as a function of pH (A) and (B) two-layer electrode, tizanidine concentration (A)  $1 \times 10^{-4}$  M and (B)  $1 \times 10^{-3}$  M, (C) uncovered graphite rod, (D) graphite rod covered with poly(4,4'-biphenol)

TABLE 2

Selectivity coefficients of the tizanidine-selective conventional electrode

Interfering species ( <i>J</i> )	Concentration (M)	$K_{\text{tizanidine } J}^{\text{Pot}}$
2,1,3-Benzothiadiazole	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
4-Amino-2,1,3-benzothiadiazole	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Mephensine <sup>a</sup>	$1 \times 10^{-2}$	$< 1 \times 10^{-4}$
Thiocholchicoside <sup>a</sup>	$9.6 \times 10^{-4}$	$< 1 \times 10^{-4}$
Chloromezanone <sup>a</sup>	$2.2 \times 10^{-3}$	$< 1 \times 10^{-4}$
Dantrolene <sup>a</sup>	$6.9 \times 10^{-3}$	$< 1 \times 10^{-4}$
Acetylsalicylic acid	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Paracetamol	$6.6 \times 10^{-3}$	$< 1 \times 10^{-4}$
2-Imidazolidone	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Pyruvic acid	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Glutamic acid	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Ascorbic acid	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Caffeine	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Urea	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Benzidine	$1 \times 10^{-3}$	$7.9 \times 10^{-2}$
Ephedrine HCl	$1 \times 10^{-3}$	$1.9 \times 10^{-2}$
Phenazone	$1 \times 10^{-3}$	$3.0 \times 10^{-3}$
Promethazine HCl	$1 \times 10^{-3}$	56
Methixene HCl	$1 \times 10^{-3}$	457
Trazodone	$1 \times 10^{-3}$	77
Pyridoxine HCl	$1 \times 10^{-3}$	$3.9 \times 10^{-3}$
L-Cysteine ethyl ester HCl	$1 \times 10^{-3}$	$4.0 \times 10^{-3}$
Sodium ion	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$
Potassium ion	$1 \times 10^{-3}$	$< 1 \times 10^{-4}$

<sup>a</sup> Pharmacological behaviour similar to tizanidine

poly(4,4'-biphenol) layer is probably due to selective permeability of this film towards protons

#### *Selectivity of the electrode*

Owing to its higher reproducibility, the conventional electrode was chosen to assess the selectivity of the tizanidine sensor and its possible use in drug analyses. The influence of organic and inorganic interfering compounds on the electrode response can be expressed by the empirical equation of Nikolskii [3]. The mixed solutions method was used to determine the experimental selectivity coefficients. This method is recommended by IUPAC as the most accurate and has been described previously [41]. It was found that the  $K_{\text{tizanidine},j}^{\text{pot}}$  values are lower than  $1 \times 10^{-4}$  when a  $1 \times 10^{-3}$  M concentration of the interfering compound does not alter the calibration graph in the linearity range of the electrode. High sensitivity coefficients related to strong interferences were determined using the separated method as no calibration graph can be established in such instances.

These coefficients, given in Table 2, show severe interferences from methixene, promethazine and trazodone, which however are not structurally related to tizanidine, but these drug are never associated with tizanidine in pharmaceutical formulations and do not influence the analytical results. On the other hand, these interfering compounds do not affect the electrode behaviour, its initial potential being immediately restored after rinsing, without any regeneration procedure.

Several compounds exhibiting similar pharmacological properties were also tested but they have no adverse effect on tizanidine determinations, even dantrolene, which includes an imidazole moiety in its structure.

Finally, 2,1,3-benzothiadiazole and its 4-amino derivative, which represent the main part of the tizanidine structure, do not influence the response of the electrode.

#### *Application to drug analysis*

Direct potentiometry was applied, without any pretreatment or extraction, to the determination of tizanidine hydrochloride in Sirdalud tablets

TABLE 3

Determination of tizanidine in Sirdalud tablets<sup>a</sup>

Theory (mg)	Found <sup>b</sup> (mg)	Recovery (%)	RSD (%)
2 000	2 058	102.9	0.82
1 500	1 535	102.3	0.85
1 000	1 035	103.5	1.79
0 500	0 511	102.2	1.40
	Mean	102.8	1.20

<sup>a</sup> Ionoprocessor calibrated between  $1 \times 10^{-3}$  and  $1 \times 10^{-4}$  M. Slope: 57.6 mV per decade. <sup>b</sup> Means of five measurements.

(containing 4 mg of the drug expressed in the base form). Twenty tablets were crushed and mixed in a mortar. An aliquot of this sample was introduced into the cell containing 10 ml of buffer and sonicated to complete the dissolution of the drug. The amount of crushed materials was selected to be compatible with the calibration range of the Ionoprocessor (the linear portion of the calibration graph where the Ionoprocessor was programmed to convert the potential response into concentration units). The results, summarized in Table 3, are in good agreement with the theoretical values and demonstrate the usefulness of the conventional electrode for the rapid and accurate determination of tizanidine in pharmaceutical formulations.

#### *Conclusion*

Three different models of electrodes selective for tizanidine were constructed and their respective characteristics determined. Several factors limiting their performance were discussed. Correlations were established between the model and the lifetime of the electrodes and between the stability of the potential and the nature of the internal contact. Additional hypotheses about the origin of the internal potential have been suggested. The electrode equipped with a classical internal reference has been successfully applied to the determination of tizanidine in pharmaceutical formulations.

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