

Construction and evaluation of PVC conventional and tubular tripeleennamine-selective electrodes: their application in pharmaceutical preparations¹

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Abstract

The construction and evaluation of tripeleennamine conventionally-shaped ion-selective electrodes and tubular detectors for the determination of this compound in pharmaceutical formulations are described.

Electrodes with conventional configuration have been constructed without an internal reference solution, using several types of immobilized ionic sensors in PVC. The different electrode membranes were prepared by using tripeleennamine tetraphenylborate as ionic-exchanger, dissolved in 2-nitrophenyl octyl ether (type A), dibutylphthalate (type B) and bis-(2-ethylhexyl)sebacate (type C) as plasticizer solvents.

The general working characteristics of the different types of conventional electrodes were evaluated in tripeleennamine solutions, with adjusted ionic strength, showing a linear response in the concentration range of about 4×10^{-5} – 1×10^{-1} M and a slope near the theoretical value. The electrodes presented a fast response (> 20 s) and a high reproducibility (± 0.2 mV per day).

The electrode selectivity in the presence of some interferences, such as sodium, potassium, lithium, ammonium, chlorpheniramine, diphenhydramine, promethazine, meclizine and pentazocine, was good, particularly for those whose sensor membrane was prepared with tripeleennamine tetraphenylborate dissolved in 2-nitrophenyl octyl ether (type A). Tubular detectors were also prepared using the same sensor membrane and were evaluated in a low-dispersion flow-injection manifold. Under these conditions the detectors presented response characteristics similar to those of the corresponding conventionally-shaped electrodes.

The analysis of different pharmaceutical forms (creams, syrups and gels) gave good results with mean recoveries of 99.8–100.6% when the experiments were conducted by direct potentiometry and 99.9–100.4% where the same determinations were conducted by flow-injection analysis with tubular detectors.

Keywords: Tripeleennamine; Pharmaceutical preparations; Ion-selective electrode; Potentiometry; Antihistaminic; Flow-injection analysis

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1. Introduction

Tripeleennamine hydrochloride is an ethylenodi-

aminic derivative used as an antihistaminic because of its H_1 -blocking effect [1].

The official methods for the determination of tripeleminamine hydrochloride in tablets are based on the extraction of the alkaline form of the compound followed by its spectrophotometric determination at 313 nm [2]. However, in the official monographs, methods of other types of formulation, such as syrups, gels and creams, are not specified. The gas chromatographic technique [3] applied to postmortem tissues was also mentioned as an alternative methodology. These techniques involve the use of complex procedures and several sample manipulations, requiring long analysis times. Besides, none of them are easy to automate.

It is common nowadays to use ion-selective electrodes of conventional configuration in the determination of drugs in pharmaceutical preparations by direct potentiometry [4] or with potentiometric detectors, namely tubular electrodes incorporated in automatic systems for flow-injection analyses (FIA) [5–9]. These methodologies are well known and well established and they may be an advantageous alternative to the time-consuming and tedious procedures suggested in pharmacopoeias such as the USP [2]. Since no complex sample preparation is required for the potentiometric technique they allow the analysis to be conducted in real time, if the FIA technique is applied; this is a major advantage in controlling and verifying pharmaceutical preparations.

No reference to a tripeleminamine-selective electrode has been found in the literature. This fact justified the construction and evaluation of this type of electrode with adequate characteristics for the analysis of medicinal products. Hence, conventionally-shaped electrodes, without inner reference solution and with a PVC membrane based on tripeleminamine tetraphenylborate and different mediator solvents, were constructed and evaluated. In accordance with their working characteristics, the best sensor membrane was selected for the construction of tubular electrodes in order to perform automatic determinations of distinct pharmaceutical forms by FIA.

2. Experimental

2.1. Apparatus

A Crison μ pH digital potentiometer (sensitivity ± 0.1 mV) coupled with an Orion 605 switcher was used for all the potentiometric measurements.

The indicator electrode was used in conjunction with an Orion 90-02-00, silver chloride/silver, double-junction electrode. The external compartment of the latter electrode contained 0.033 M potassium sulphate since the potassium cation showed reduced interference, determined by measurement of the potentiometric selectivity coefficients.

pH measurements were carried out with a Phillips GAH 110 glass electrode and an Anatron pH meter, model 300.

2.2. Reagents and Solutions

All the reagents were of an analytical or similar quality and were used as purchased with no additional purification.

For the ion-exchange preparation sodium tetraphenylborate (Fluka ref. 72020) was used.

The more concentrated solutions were prepared by accurate weighing of the corresponding solids followed by dilution with deionized water (conductivity less than $0.1 \mu\text{S cm}^{-1}$). The less concentrated solutions were obtained from the concentrated solutions and prepared daily.

The ionic strength of all solutions was adjusted with 0.033 M potassium sulphate. For adjusting the pH and the ionic strength of the pharmaceutical samples simultaneously, a buffer solution of $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ (pH 7.0; $I = 0.1$ M) was used.

2.3. Preparation of conventionally-shaped and tubular electrodes

The ionic-exchange agent, tripeleminamine tetraphenylborate, was prepared by a precipitation reaction between 50 ml of 0.01 M tripeleminamine hydrochloride and 100 ml of 0.01 M sodium tetraphenylborate. The precipitate was filtered, washed with ether, dried and kept in a dark chamber.

Table 1
Membrane composition of the conventionally-shaped tripele-
namine-selective electrodes

Components	Membrane composition (%w/w)		
	Type A	Type B	Type C
Tripele- namine tetraphenylborate	1.65	0.30	0.30
2-Nitrophenyl octyl ether	69.40	–	–
Dibutylphthalate	–	68.62	–
Bis-(2-ethylhexyl)sebacate	–	–	68.40
PVC	28.95	31.08	31.30

Different sensor solutions were prepared by dissolving about 0.04 g of the dried precipitate in 2.0 g of 2-nitrophenyl octyl ether (type A electrode); 9.0 g of dibutylphthalate (type B electrode); or 9.0 g of bis-(2-ethylhexyl) sebacate (type C electrode). Different sensor solutions were prepared using several mediator solvents to study their influence on electrode behaviour, mainly in respect to selectivity.

The electrode membranes were obtained by immobilizing 0.4 ml of the referred sensor solutions with 0.18 g of poly (vinylchloride) (PVC) previously diluted in about 6 ml of tetrahydrofuran. Table 1 shows the composition of the different prepared membranes.

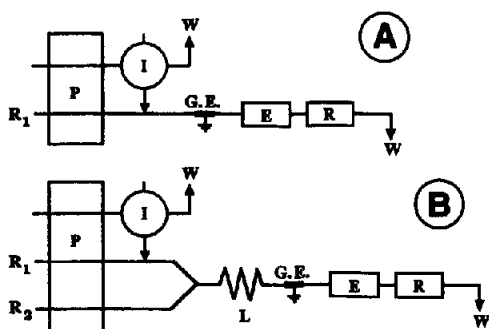


Fig. 1. Flow-injection manifolds used for tubular electrode evaluation (A) and for tripele-
namine determination in pharmaceutical preparations (B). P, peristaltic pump; I, injection valve (loop 170 μ l); GE, grounding electrode; L, dilution coil (32 cm for (A) and 37 cm for (B)); E, tubular electrode; R, reference electrode; W, waste; R₁, carrier solution; R₂, pH and ionic strength adjuster. The total flow rate of 6.0 ml min⁻¹.

The conventionally-shaped electrodes (types A, B and C), were prepared by applying the sensor membranes dropwise over an epoxy resin and graphite support, following the previously described procedures [10]. The tubular electrodes were constructed according to the method of Alegret et al. [11] by using the type A sensor membrane.

2.4. Procedures for the direct potentiometric and FIA assay of pharmaceutical preparations

Different commercial pharmaceutical formulations (syrup, cream and gel) were used for the determination of tripele-
namine by direct potentiometry.

For the preparation of the sample an amount of the product, in which the content of tripele-
namine hydrochloride was equivalent to about 0.02 g, was weighed and dissolved in a buffer solution of KH₂PO₄/K₂HPO₄ (pH 7.0; I = 0.1 M) in a 20 ml volumetric flask.

From each of the prepared samples, a volume equivalent to 1 ml was diluted with the buffer to a final volume of 25 ml in order to obtain solutions of approximately 1×10^{-4} M tripele-
namine.

The quality of the results obtained by both direct potentiometry and FIA was evaluated by determination of sample recoveries. Thus, to the previously prepared samples, 50 μ l of 0.5 M tripele-
namine hydrochloride was added, in order to obtain a final concentration of about 1×10^{-3} M.

When the samples were analyzed by FIA, they were initially diluted with water, as the pH and ionic strength adjustments were achieved in the interior of the manifold.

2.5. FIA manifolds

In the FIA systems, the solutions were all pumped by Gilson Minipuls 3 peristaltic pumps and samples were inserted into the manifold through a four-way Rheodyne 5020 rotating valve. In the established assemblages several home-made Perspex devices, namely confluences, reference and tubular electrode supports and grounding electrodes were used [6]. These ele-

Table 2

Working response characteristics for tripeleppamine conventionally-shaped and tubular electrodes without an inner reference solution, in (I) solutions with ionic strength adjusted with 0.033 M K_2SO_4 and in (II) KH_2PO_4/K_2HPO_4 buffer solutions (pH 7.0; 0.1 M)

Characteristic	Conventionally-shaped electrodes						Tubular electrodes
	Type A		Type B		Type C		Type A
	I	II	I	II	I	II	Single channel
LLLR ^a (M)	4.0×10^{-5}	4.0×10^{-5}	4.0×10^{-5}	4.0×10^{-5}	4.0×10^{-5}	5.7×10^{-5}	5.0×10^{-6}
PDL ^b (M)	2.3×10^{-5}	2.8×10^{-5}	2.3×10^{-5}	2.3×10^{-5}	2.1×10^{-5}	2.7×10^{-5}	–
Slope (mV decade ⁻¹)	57.8 ± 0.1	52.5 ± 0.3	56.8 ± 0.1	52.9 ± 1.2	57.4 ± 0.3	54.6 ± 1.2	58.9 ± 0.2
Reproducibility (mV)	± 0.2	± 0.2	± 0.2	± 0.2	± 0.2	± 1.0	± 2.0
Response time (s)	<20	<20	<20	<20	<20	<20	–
Lifetime (months)		>9		≈ 3		≈ 3	>9

^aLLLR = lower limit of linear range.

^bPDL = practical detection limit.

ments were connected by using teflon tubes (0.8 mm i.d.).

The results obtained by FIA were recorded with a Kipp & Zonen recorder, model BD 111, coupled to the millivoltmeter.

The general working characteristics of the tubular detectors whose membranes contained tripeleppamine tetraphenylborate dissolved in 2-nitrophenyl octyl ether were assessed in low-dispersion single channel FIA manifold (Fig. 1A). 0.033 M potassium sulphate was used as the carrier. In order to stabilize the baseline a fixed tripeleppamine concentration (1×10^{-7} M) was used.

In order to compare the intrinsic operating characteristics of the tubular electrodes with those of the conventional type a low-dispersion manifold was constructed and optimized by a univariate process. For this purpose, several parameters, injection volume, flow rate and dilution coil length, were tested. An injection volume of 170 μ l, a flow rate of 6.0 ml min⁻¹ and a 32 cm dilution coil were used. Under these conditions the analytical signal was about 95% of the corresponding steady state with a sampling rate that was sufficiently high.

For the automatic determination of tripeleppamine in pharmaceutical products, a double-channel FIA system (Fig. 1B) was set up to obtain direct pH and ionic strength adjustment inside the

manifold. Thus, for creating experimental conditions which would mimic those used for a single channel manifold a 37 cm dilution coil, an injection volume of 170 μ l and an overall flow rate of 6.0 ml min⁻¹ were used. A carrier solution with a fixed tripeleppamine concentration (2×10^{-7} M), double that used in the single channel system, was pumped through the principal channel. Through the auxiliary channel a KH_2PO_4/K_2HPO_4 (pH 7.0; $I = 0.2$ M) buffer solution was introduced and merged with the carrier at the confluence point.

3. Results and discussion

3.1. Behaviour of the conventionally-shaped electrodes

The general working characteristics of the different conventionally-shaped (Table 2) were evaluated by repeated calibration curves [12] using tripeleppamine solutions with the ionic strength adjusted to 0.1 M or with phosphate buffer solution in a concentration range 4×10^{-6} – 1×10^{-1} M. Under these experimental conditions, the various electrodes were satisfactory with very similar working parameters (Table 2).

The electrode response was almost instantaneous (less than 20 s) with excellent reproducible potential values (± 0.2 mV per day). These char-

Table 3
Potentiometric selectivity coefficients ($\log K^{\text{POT}}$)^a for tripeleppamine conventionally-shaped electrodes

Interferent	Concentration (M)	Type of electrode		
		A	B	C
Sodium	1.0×10^{-4}	-1.55 ± 0.06	-1.44 ± 0.06	-0.75 ± 0.14
	1.0×10^{-3}	-2.81 ± 0.15	-2.71 ± 0.11	-2.22 ± 0.16
Potassium	1.0×10^{-4}	-1.80 ± 0.10	-1.23 ± 0.05	-1.48 ± 0.25
	1.0×10^{-3}	-2.93 ± 0.12	-2.51 ± 0.03	-2.76 ± 0.16
Lithium	1.0×10^{-4}	-1.67 ± 0.06	-1.45 ± 0.05	-1.48 ± 0.02
	1.0×10^{-3}	-2.79 ± 0.06	-2.60 ± 0.19	-2.77 ± 0.13
Ammonium	1.0×10^{-4}	-1.59 ± 0.09	-1.14 ± 0.11	-1.25 ± 0.11
	1.0×10^{-3}	-2.75 ± 0.08	-2.50 ± 0.10	-2.61 ± 0.01
Chlorpheniramine	1.0×10^{-4}	-0.76 ± 0.07	-0.50 ± 0.04	-0.63 ± 0.07
	1.0×10^{-3}	-1.10 ± 0.04	-0.75 ± 0.03	-0.79 ± 0.02
Diphenhydramine	1.0×10^{-4}	-0.68 ± 0.05	-0.21 ± 0.02	-0.14 ± 0.07
	1.0×10^{-3}	-1.05 ± 0.03	-0.36 ± 0.01	-0.17 ± 0.13
Promethazine	1.0×10^{-4}	-0.36 ± 0.05	$+0.13 \pm 0.02$	$+0.46 \pm 0.12$
	1.0×10^{-3}	-0.62 ± 0.04	$+0.25 \pm 0.03$	$+0.61 \pm 0.21$
Meclizine	1.0×10^{-4}	$+0.18 \pm 0.27$	$+2.02 \pm 0.55$	$+2.12 \pm 0.53$
	1.0×10^{-3}	$+0.42 \pm 0.26$	$+3.45 \pm 0.91$	$+2.65 \pm 0.21$
Pentazocine	1.0×10^{-4}	-0.50 ± 0.14	-0.28 ± 0.07	-0.29 ± 0.03
	1.0×10^{-3}	-1.33 ± 0.09	-0.52 ± 0.04	-0.32 ± 0.03

^aMean and standard deviation of four determinations with two electrodes.

acteristics are adequate for their use in direct potentiometric determinations.

The potentiometric selectivity coefficients ($\log K^{\text{POT}}$) towards some common inorganic cations or organic cations with similar structure were evaluated for concentrations of 1×10^{-4} and 1×10^{-3} M (Table 3) by the separated solution method [12].

The influence of pH on electrode potential was determined in 1×10^{-4} M and 1×10^{-3} M tripeleppamine solutions with adjusted ionic strength (Fig. 2). The pH changes were obtained by adding hydrochloric acid and potassium hydroxide as concentrated solutions. The extension of the operational potential ranges for the different electrodes was similar and about 4.7–7.5 units

when the concentration of the main ion in the solution was 1×10^{-4} M. For the more concentrated solutions (1×10^{-3} M) a slight increase in the pH range was registered, and shown in Fig. 2.

From the results presented in Tables 2 and 3, it was concluded that the use of the different mediator solvents in the membrane preparation influences the selectivity and durability of the electrodes. The units prepared with 2-nitrophenyl octyl ether as plasticizer showed more stability, selectivity and durability (>9 months) when compared with the other types. The excellent characteristics of type A electrodes justified their selection for the analytical applications performed, especially for complex matrices like pharmaceuticals.

Table 4

Tripelennamine determination^a in some pharmaceutical preparations using conventionally-shaped electrodes with direct potentiometry and tubular electrodes with FIA

Pharmaceutical Preparation (nominal content)	Conventionally-shaped electrodes		Tubular electrodes	
	Found (%w/w)	%Recovery	Found (%w/w)	%Recovery
Cream (2.0%)	2.29 ± 0.17	99.77 ± 0.46	1.96 ± 0.05	100.38 ± 0.42
Syrup (0.5%)	0.48 ± 0.03	100.40 ± 2.03	0.49 ± 0.01	99.99 ± 0.41
Gel (2.0%)	2.19 ± 0.07	100.60 ± 0.77	2.03 ± 0.08	99.90 ± 0.55

^aMean and standard deviation of eight determinations with three electrodes.

3.2. Behaviour of the tubular electrodes

The tubular electrodes were prepared by employing type A sensor solution as the solution offered suitable characteristics, especially durability, for use in a continuous flow system.

The operating characteristics of these electrodes, when evaluated in the low-dispersion manifold (Fig. 1A) with 0.033 M K₂SO₄, are not very different from those obtained in batch conditions and sometimes even better, especially where the higher slope (58.9 mV per decade) and lower limit of linear response (5×10^{-6} M) are considered (see also Table 2).

The potentiometric selectivity coefficients towards different interferences were determined by a similar procedure to the separated solutions method used for the evaluation of conventionally shaped electrodes [12] and for the same concentrations. The calculated values do not differ from those obtained with the conventionally-shaped electrodes, presented in Table 3.

To test the influence of pH in detector potential, the same manifold with small modifications [13] was used. The operational pH intervals found were 4.9–8.6 and 4.9–7.7 for tripelennamine concentrations of 1×10^{-3} M and 1×10^{-4} M respectively (Fig. 2).

The characteristics of the tubular detectors permitted expeditious determinations of tripelennamine in pharmaceutical preparations, with sampling rates of about 145 samples per hour (Fig. 3).

3.3. Analysis of tripelennamine in pharmaceutical formulations

Tripelennamine determinations in different pharmaceutical formulations (creams, syrups and gels) were performed on the previously prepared samples by direct potentiometry with conventionally-shaped electrodes and by FIA (Fig. 3) with the respective tubular detectors. The averages of the concentrations obtained for each sample and the corresponding standard deviations are shown in Table 4. To evaluate the quality of the results,

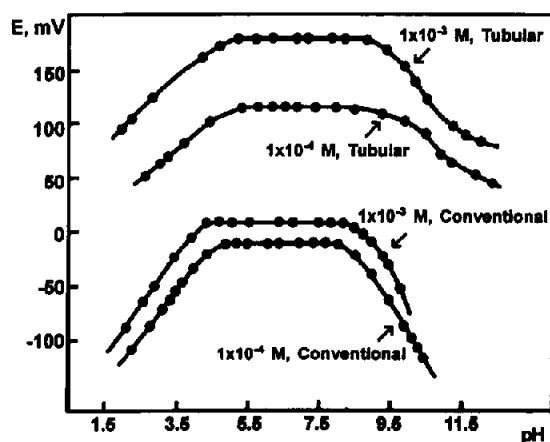


Fig. 2. Plots of potential vs. pH for type A conventionally-shaped (Conventional) and tubular (Tubular) electrodes in 1×10^{-4} M and 1×10^{-3} M tripelennamine hydrochloride.

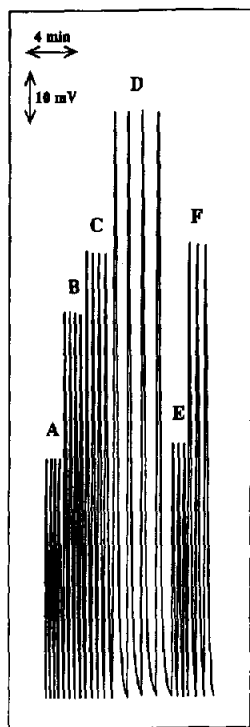


Fig. 3. A FIA record obtained with the tubular electrode by the injection of different standard tripeleannamine solutions ((A) = 1×10^{-4} M; (B) = 5×10^{-4} M; (C) = 1×10^{-3} M; (D) = 5×10^{-3} M), a real sample (E) and its recovery (F), for the determination of tripeleannamine in a pharmaceutical cream.

recovery values were also determined and are presented in the same table.

4. Conclusions

The tripeleannamine-selective conventionally-shaped electrodes prepared with different mediator solvents shared good operating characteristics, namely a low practical detection limit, good reproducibility, a large linear range and good selectivity towards several inorganic and organic cations.

The use of different plasticizer solvents in the construction of the electrodes led to significant differences in their working characteristics, especially in terms of selectivity, reproducibility and durability. The electrodes prepared with 2-nitrophenyl octyl ether showed the best overall charac-

teristics and the correspondent tubular electrodes behaved similarly. With a simple manifold it was possible to obtain high sampling rates (about 145 determinations per hour).

The analysis of several pharmaceutical preparations, using both conventionally-shaped and tubular electrodes, gave comparable results with high accuracy.

Simple potentiometric methods using these types of electrodes allowed quick results, especially in the FIA system, with no need for the tedious procedures for sample preparations that are necessary with the official methods. The characteristics are very attractive to the pharmaceutical industry and may lead to new developments in the routine quality control of its products.

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