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Talanta 69 (2006) 481–487
Talanta
www.elsevier.com/locate/talanta

Flow injection potentiometric determination of clobutinol hydrochloride

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Received 17 August 2005; received in revised form 13 October 2005; accepted 14 October 2005
Available online 21 November 2005

Abstract

New clobutinol (Clob) ion-selective polyvinyl chloride (PVC) membrane electrodes, based on the ion-associates of Clob with phosphotungstic acid or phosphomolybdic acid were prepared using dibutyl phthalate as plasticizing solvent. The electrodes were characterized in terms of membrane composition, temperature and pH. The sensors showed a near-Nernstian response over the concentration ranges (6.31×10^{-6})–(1.00×10^{-2}) and (5.01×10^{-5})–(1.00×10^{-2}) M in the case of clobutinol-phosphotungstate ($(Clob)_3$-PT) applying batch and flow injection (FI) analysis, respectively, and (1.58×10^{-5})–(1.00×10^{-2}) and (5.01×10^{-5})–(1.00×10^{-2}) M in case of clobutinol-phosphomolybdate ($(Clob)_3$-PM) for batch and FI analysis systems, respectively. The electrodes were successfully applied for the potentiometric determination of ClobCl in pharmaceutical preparation and urine in steady state and flow injection conditions. The electrodes exhibit good selectivity for Clob with respect to a large number of inorganic cations, sugars and amino acids.

Keywords: Clobutinol hydrochloride; Ion-selective electrodes; Flow injection analysis; Potentiometry

1. Introduction

Clobutinol hydrochloride, 2-(4-chlorobenzyl)-3-(dimethylaminomethyl) butan-2-ol hydrochloride [1215-83-4], is widely used as a centrally acting cough suppressant for non-productive cough [1,2]. It is effective and safe in recommended daily dose for cough in cancer and advanced cancer cough [3]. Clobutinol hydrochloride is not cited in any pharmacopoeia and a literature survey reveals that the number of the analytical methods referring to the drug is relatively limited. The drug has been determined in biological fluids by gas chromatography using surface ionization detection [4]. Derivative UV spectrophotometric and high performance liquid chromatographic (HPLC) methods have been developed by Malliou et al. [5]. Recently, a HPLC method was reported to determine simultaneously the drug together with some anti-inflammatory drugs in urine [6]. A potentiometric ion-selective electrode method based on clobutinol-tetraphenyl borate has been reported [7]. Ion-selective membrane electrodes play an increasing role in pharmaceutical analysis with further use in FI [8–10] offering advantages of simplicity, rapidity and accuracy. In the present work, several plastic membrane selective electrodes have been constructed. The electrodes are based on incorporation of clobutinol-phosphotungstate ($(Clob)_3$-PT) or clobutinol-phosphomolybdate ($(Clob)_3$-PM) ion exchangers in polyvinyl chloride (PVC) plasticized with dibutyl phthalate (DBP). The performance of these electrodes was examined with regard to sensitivity, selectivity, pH effect, response time, and other factors. Applications of these electrodes to the determination of ClobCl in pharmaceutical preparation and urine samples for batch and FI systems were being described.

2. Experimental

2.1. Reagents and materials

All chemicals were of analytical grade. Double distilled water was used throughout all experiments. Pure grade clobutinol hydrochloride and the pharmaceutical preparation Silomat® tablets were provided by Chemical Industries Development Co. (CID), Cairo, Egypt. Phosphotungstic acid (PTA), phosphomolybdic acid (PMA), dioctyl sebacate (DOS), and tricresyl phosphate (TCP) were from Fluka, tetrahydrofuran (THF), DBP,

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doi:10.1016/j.talanta.2005.10.018

and dioctyl phthalate (DOP) from Merck. PVC of relatively high molecular weight was from Aldrich.

Aqueous solution of PTA was prepared and the exact concentration of the solution was determined by the appropriate recommended method [11].

2.2. Apparatus

Potentiometric and pH measurements were carried out using a digital Schott Gerate pH meter, Model CG 820. A Techne (Cambridge, UK) Model C-100 circulator thermostat was used to control the temperature of the test solutions. A saturated calomel electrode (SCE) was used as the external reference, while a Ag/AgCl electrode served as an internal reference. The electrochemical system of the conventional electrode may be represented as follows: Ag/AgCl/filling solution/membrane/test solution//KCl salt bridge//saturated calomel electrode.

The flow injection setup was composed of a four-channel peristaltic pump (Ismatec ISM 827, Zurich, Switzerland) and an injection valve model 5020 with exchangeable sample loop from Rheodyne (Cotati, CA, USA). The electrodes were connected to a WTW pMX 2000 microprocessor mV/ion meter and interfaced to a Model BD111 strip chart recorder from Kipp and Zonen (Delft, The Netherlands).

A wall-jet cell, providing a low dead volume, fast response, good wash characteristics, ease of construction, and compatibility with electrodes of various shapes and sizes, was used in flow measurements. A Perspex cup with axially positioned inlet polypropylene tubing was mounted at the sensing surface of the electrode body. The optimized distance between the nozzle and the sensing surface of the electrode was approximately 3 mm. The ion-selective electrode with flow cup, reference electrode (SCE) and the outlet tube were placed in a beaker, where the level of solution was kept 1 cm above the electrode surface. Fig. 1 represents the schematic diagram of the flow injection system used in the measurements. The flow injection measurements were carried out in a two-line system; the sample was injected into a distilled water stream, which then merged with another stream of distilled water. In both lines, the same tubing size was used, offering the same flow rate. The connector of the two streams was linked to the detector by a 50 cm tube of 0.4 mm internal diameter.

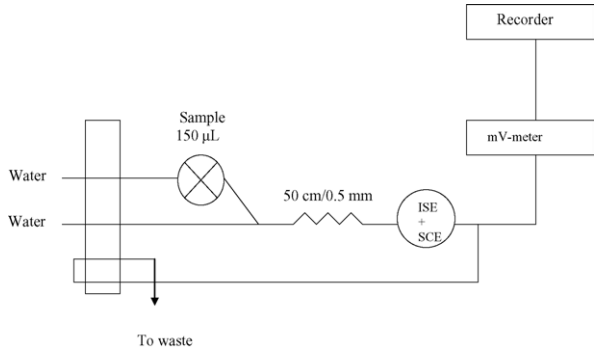

Fig. 1. Schematic diagram of the flow injection system used in the measurements.

2.3. Preparation of the ion exchangers

The ion exchangers, $(Clob)_3$-PT and $(Clob)_3$-PM, were prepared by mixing 150 ml of 10^{-2} M ClobCl solution to 50 ml of 10^{-2} M of each of phosphotungstic acid or phosphomolybdic acid, respectively. The formed precipitates were filtered, washed thoroughly with distilled water until chloride free and dried at room temperature. The composition of the ion exchangers was found to be 3:1 both in case of $(Clob)_3$-PT and $(Clob)_3$-PM, as confirmed by elemental analysis data done at microanalytical research laboratory in National Research Centre (Dokki, Cairo, Egypt). The percentage values found are 14.10, 2.03, and 1.11 and the calculated values are 13.84, 1.83, and 1.15 for C, H, and N, respectively, in case of $(Clob)_3$-PT, while in case of $(Clob)_3$-PM the percentage values found are 19.80, 2.53, and 1.60 and the calculated are 19.48, 2.57, and 1.62 for C, H, and N, respectively.

2.4. Electrode preparation

The electrode was constructed as described previously [12]. The membrane composition was studied by varying the percentages (w/w) of the ion exchanger, polyvinyl chloride (PVC) and DBP, until the optimum composition that exhibits the best performance characteristics was obtained. The membranes were prepared by dissolving the required amount of the ion exchanger, PVC and DBP, in about 10 ml of THF. The solution mixture was poured into a 6.0 cm Petri dish and left to dry in air. To obtain a uniform membrane thickness, the amount of THF was kept constant, and its evaporation was fixed for 24 h. The thickness of the membrane was about 0.2 mm. A 12 mm diameter disk was cut out from the prepared membrane and glued using PVC–THF paste to the polished end of a plastic cap attached to a glass tube. The electrode body was filled with a solution of 1×10^{-1} M NaCl and 1×10^{-2} M ClobCl. The electrode was preconditioned before use by soaking in a 1×10^{-3} M ClobCl solution.

2.5. Selectivity of the electrodes

The selectivity coefficients were determined by the separate solutions method (SSM) [13], in which the Nicolsky Eisenman equation was used:

$$\log K^{\mathrm{Pot}}_{\mathrm{Clob},J^{Z+}} = \frac{E_2 - E_1}{S} + \log[\mathrm{Clob}] - \log[J^{Z+}]^{1/z}$$

where E_1 and E_2 are the electrode potentials in a 1×10^{-3} M solutions of ClobCl and interfering ions J^{Z+}, respectively, and S is the slope of the calibration graphs in mV decade^{-1}.

In FI, a series of standard ClobCl solutions of concentrations between 10^{-5} and 10^{-2} M was prepared, their corresponding peak heights were measured and used to determine the slope of the calibration graph. Solutions that are 1×10^{-3} M of interfering ions were prepared, their corresponding peak heights were also measured. The selectivity coefficients were calculated using the above equation.

The selectivity coefficients in case of species without charges were determined by the matched potential method (MPM) [14]. In this method, the selectivity coefficient is defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions. At first, a known activity (a_{drug}) of the primary ion solution is added into a reference solution that contains a fixed activity of primary ions, and the corresponding potential change (ΔE) is recorded. Next, a solution of an interfering species is added to the reference solution until the same potential change (ΔE) is recorded. The change in potential produced at the constant background of the primary ion must be the same in both cases.

$$K^{pot}_{Clob,J^{Z+}} = \frac{a_{drug}}{a_J}$$

where a_J is the activity of the added interferent.

2.6. Potentiometric determination of ClobCl

ClobCl has been determined potentiometrically using the investigated electrodes by the standard addition method [15].

In standard addition method, known small increments of 1×10^{-1} M standard ClobCl solution were added to 50.0 ml aliquot samples of various concentrations ((8×10^{-5})–(8×10^{-4}) M) of pure drug or pharmaceutical preparations Silomat® tablets. The change in millivolt readings was recorded for each increment and used to calculate the concentration of ClobCl sample solution using the following equation:

$$C_x = C_s \left(\frac{V_s}{V_x + V_s}\right) \left(10^{n(\Delta E/S)} - \frac{V_x}{V_x + V_s}\right)^{-1}$$

where C_x and V_x are the concentration and the volume of the unknown, respectively, C_s and V_s the concentration and volume of the standard, respectively, S the slope of the calibration graph and ΔE is the change in millivolt due to the addition of the standard.

2.7. Determination of ClobCl in pharmaceutical preparation Silomat® tablets

Twenty tablets were accurately weighed and powdered in a mortar, the required amount from the tablet powder was dissolved in about 30 ml bidistilled water and filtered in a 50-ml measuring flask. The residue was washed three times with bidistilled water; the volume was completed to the mark by the same solvent. The contents of the measuring flask were transferred into a 100-ml beaker, and subjected to potentiometric determination of ClobCl.

In FI, a series of solutions of different concentrations was prepared from the tablets and the peak heights were measured, and then compared with those obtained from injecting a standard solution of the same concentration prepared from pure ClobCl.

2.8. Determination of ClobCl in spiked urine samples

Different amounts of ClobCl and 5 ml of urine of a healthy person were transferred to 50-ml measuring flask and completed to the mark by bidistilled water. The contents of the measuring flask were transferred to a 100-ml beaker, and subjected to potentiometric determination of ClobCl by the standard additions method. In FI, the procedure was as previously described in case of tablets.

2.9. Potentiometric titration of ClobCl

An aliquot of ClobCl ((1.80×10^{-3})–(3.00×10^{-3}) M) was transferred into a 100 ml beaker and the solution was diluted to 50 ml with bidistilled water and then titrated against a standard solution of PTA using the investigated electrodes as indicator electrodes. The same method was applied for determination of the pharmaceutical tablets.

3. Results and discussion

3.1. Optimization of the electrodes in batch conditions

3.1.1. Composition of the membranes

Four membrane compositions were prepared by varying the percentage of the ion exchangers $(Clob)_3$-PT and $(Clob)_3$-PM (Table 1). The results showed that the electrode made by membrane with 12% $(Clob)_3$-PT or 5% $(Clob)_3$-PM ion exchangers exhibited the best performance characteristics (slope, 57.3 mV concentration decade^{-1}, at 25 °C; usable concentration range, (6.31×10^{-6})–(1.00×10^{-2}) M ClobCl; detection limit [16], 4.5×10^{-6} M, and response time, ≤10 s) for $(Clob)_3$-PT electrode. For the $(Clob)_3$-PM electrode the characteristics are: slope, 60.0 mV concentration decade^{-1}, at 25 °C; usable concentration range, (1.58×10^{-5})–(1.00×10^{-2}) M ClobCl; detection limit, 5.0×10^{-6} M, and response time, ≤10 s.

3.1.2. Effect of solvent mediator

Four plasticizers, DBP, DOP, DOS, and TCP, were examined (Table 2). The results reveal that DBP is the best of the plasticizers tested. Poor sensitivities for the electrodes plasticized by DOP, DOS, and TCP are due to low solubilities or low distributions of $(Clob)_3$-PT or $(Clob)_3$-PM ion exchangers in these

Table 1
Composition of the different Clob membranes and slopes of the corresponding calibration graphs at 25 ± 1 °C and 30 min of soaking in 1×10^{-3} M ClobCl solution

Membrane	Composition (%, w/w)			Slope (mV decade^{-1})	R.S.D. (%)
	Ion associate	PVC	DBP		
Clob-PT electrodes					
I	5.0	47.5	47.5	51.5	
II	10.0	45.0	45.0	52.5	
III	12.0	44.0	44.0	57.3	0.8
IV	15.0	42.5	42.5	52.6	
Clob-PM electrodes					
I	5.0	47.5	47.5	60.0	2
II	10.0	45.0	45.0	59.5	
III	15.0	42.5	42.5	59.5	
IV	20.0	40.0	40.0	59.5	

R.S.D.: relative standard deviation (three determinations).

Table 2
Effect of plasticizers on Clob responsive membranes and slopes of the corresponding calibration graphs at 25 ± 1 °C and 30 min of soaking in 10^{-3} M ClobCl

Plasticizer	Slope (mV decade^{-1})	Usable concentration range (M)	Detection limit (M)
Clob-PT electrode			
DBP	57.3	(6.31×10^{-6})–(1×10^{-2})	4.5×10^{-6}
DOP	51.2	(6.31×10^{-6})–(1×10^{-2})	4.5×10^{-6}
DOS	54.1	(1.00×10^{-5})–(1×10^{-2})	7.9×10^{-6}
TCP	49.6	(6.31×10^{-6})–(1×10^{-2})	4.5×10^{-6}
Clob-PM electrode			
DBP	60.0	(1.58×10^{-5})–(1×10^{-2})	5.0×10^{-6}
DOP	48.9	(2.00×10^{-5})–(1×10^{-2})	6.3×10^{-6}
DOS	58.2	(1.58×10^{-5})–(1×10^{-2})	7.1×10^{-6}
TCP	50.2	(1.58×10^{-5})–(1×10^{-2})	5.0×10^{-6}

DBP: dibutyl phthalate; DOP: dioctyl phthalate; DOS: dioctyl sebasate; TCP: tricresyl phosphate.

solvents [17]. The electrodes using DBP as a plasticizer provided not only higher Nernstian slope but also a wider response, more stable potential reading and a lower limit of detection.

3.1.3. Life time of the electrodes

The performance of the electrodes was studied as a function of soaking time. Calibration plots (pClob versus *E*, mV) were obtained after the electrode was soaked continuously in 1×10^{-3} M ClobCl solution for 0.5, 2, and 8 h and 1, 2, 9, 16, 18, 30, and 47 days. The results indicate that in case of $(Clob)_3$-PT electrode, the slope of the calibration graph was 57.4 mV decade^{-1} after 1 day soaking, then decreased reaching nearly 56.0, 54.3, 52.7, and 44.2 mV decade^{-1} after 16, 23, 30, and 47 days of soaking. In case of $(Clob)_3$-PM electrode the slope of the calibration graph remained constant near 59.0 mV decade^{-1} for up to 9 days soaking, then decreased reaching 56.0, 51.8, 49.7, and 37.0 mV decade^{-1} after 16, 18, 20, and 22 days of soaking, respectively.

3.1.4. Effect of pH

The effect of pH of the test solution (10^{-4} and 10^{-3} M ClobCl) on the $(Clob)_3$-PT and $(Clob)_3$-PM electrode potentials was investigated by following the variation in potential with change in pH by addition of very small volumes of hydrochloric acid and sodium hydroxide (each 0.1–1.0 M). The results indicated that the electrode did no respond to the pH change in the range 4.0–8.5 and 4.5–8.7 for $(Clob)_3$-PT electrode and $(Clob)_3$-PM electrode, respectively (Fig. 2). The decrease occurring at higher pH values is most probably attributed to the formation of the free clobutinol base in the solution, leading to a decrease in the concentration of clobutinolium cation: a pK_a of 9.59 was reported in reference tables (Advanced Chemistry Development [ACD] software Solaris V 4.67 [Scifinder Solaris 1994–2005]).

3.1.5. Effect of temperature of the test solution

To study the thermal stability of the electrodes, calibration graphs were constructed at different test solution temperatures (25–70 °C), and the isothermal coefficients (d*E*/d*t*) of the selected electrodes were calculated [18], to be −0.0015 V/°C and of the cell to be 0.0008 V/°C. These values indicate fairly good thermal stability of the electrodes.

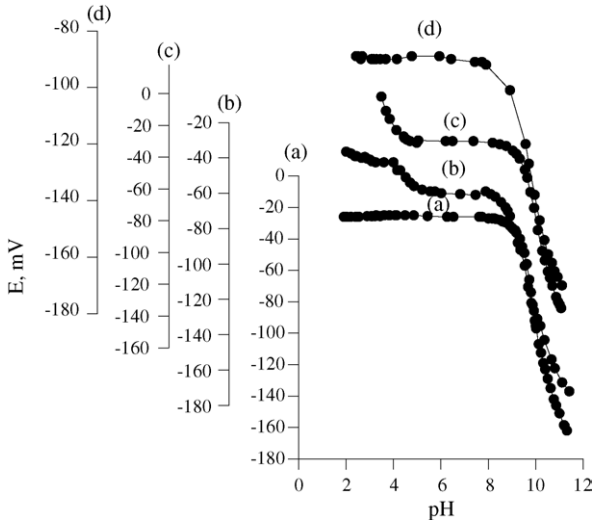

Fig. 2. Effect of the pH of the test solution containing 1×10^{-3} and 1×10^{-4} M ClobCl on the potential response of the Clob electrodes: (a and b) $(Clob)_3$-PM and (c and d) $(Clob)_3$-PT.

3.2. FI response

The dispersion coefficients were found to be 1.4 and 1.3 for $(Clob)_3$-PT and $(Clob)_3$-PM, respectively, i.e. limited dispersion that aids optimum sensitivity and fast response of the electrodes [19].

Samples of different volumes (4.70–500.0 μl) were injected. In general, the higher the sample volume, the higher the peak heights and residence time of the sample at the electrode surface, requiring a longer time to reach a steady state and greater consumption of sample [20]. A sample loop of size 150 μl was used throughout this work, giving maximum peak height, less consumption of reagents, and a short time to reach the base line.

The dependence of the peak height and time to recover the base line on flow rate was studied. The response of the two electrodes to a solution 1×10^{-3} M ClobCl was studied at different flow rates (4.15, 5.35, 7.50, 9.70, 12.50, 17.85, 23.25, 25.00, 27.00, and 30.00 ml/min). With constant injection volume (150 μl), the residence time of the sample was inversely proportional to the flow rate [21]. It was found that, as the flow rate increased, the peaks became higher and narrower until a flow rate of 12.50 and 7.50 ml/min in case of $(Clob)_3$-PT and $(Clob)_3$-PM, respectively. The peaks obtained above these flow rates were nearly the same. These flow rates were used throughout this work providing the maximum peak height, a shorter time to reach the base line and less consumption of the carrier solution.

In potentiometric detection, the electrode potential depends on the activity of the main ion sensed, but in flow conditions, the main unfavorable feature of this detection is the slow response of the electrode to concentration changes which is pronounced when low concentrations are measured [22]. An increase in the slope of the calibration plots in FI was observed compared with

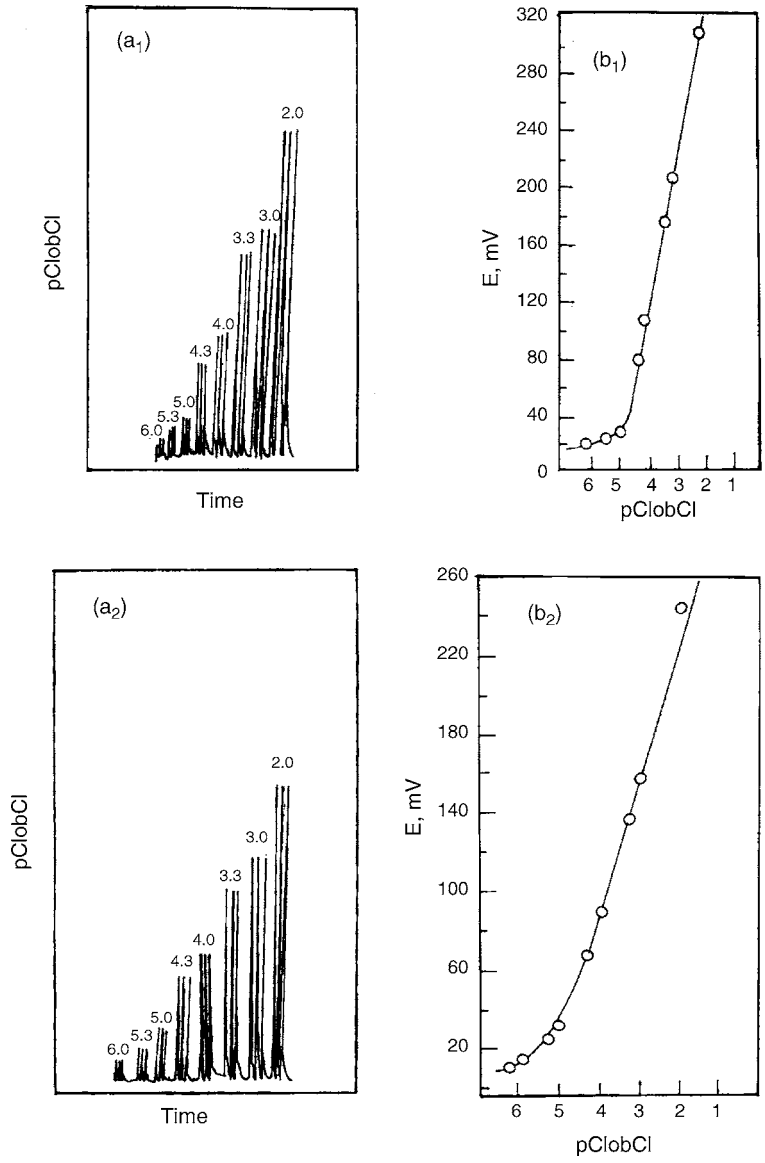

Fig. 3. Recording (a_1 and a_2) and their corresponding calibration graphs (b_1 and b_2) for $(Clob)_3$-PT and $(Clob)_3$-PM electrodes under FI conditions.

batch measurement where potential is measured under conditions very close to the equilibrium at the membrane solution interface. The slopes of the calibration graphs obtained were 88.4 and 75.5 mV concentration decade^{-1} compared to 57.3 and 60.0 mV concentration decade^{-1} in batch conditions for $(Clob)_3$-PT and $(Clob)_3$-PM electrodes, respectively. The usable concentration ranges of the electrodes in FI measurements were from 5.01×10^{-5} to 1.00×10^{-2} M for both the electrodes. The detection limits was 1.6×10^{-5} and 1.8×10^{-5} M for $(Clob)_3$-PT and $(Clob)_3$-PM, respectively, which are higher than those obtained in steady-state mode. The lower sensitivities of the electrodes in FI may be attributed to many factors such mass transport rate, the sample dispersion and the effect of contact time between the sample and the electrode [23]. In general, this behavior is similar to that presented by the authors for previously described electrode [24,25]. Fig. 3 represents typical recordings and their corresponding calibration graphs obtained for $(Clob)_3$-PT and $(Clob)_3$-PM electrodes.

3.3. Selectivity of the electrodes

The influence of some inorganic cations, sugars, amino acids, vitamins and urea on the clobutinol electrode was investigated. In FI conditions, the values of selectivity coefficients were calculated based on potential values measured at the top of the peak for the same concentrations of the drug and the interferent according to the separate solution method. The selectivity coefficients values $-\log K^{pot}_{Clob,J^{Z+}}$ of the electrodes listed in Table 3 reflect a high selectivity of these electrodes towards clobutinol cation, under both batch and FI conditions. The inorganic cations do not interfere owing to the differences in ionic size and consequently in their mobilities and permeabilities as compared with $Clob^+$. In case of non-ionic species, the high selectivity is mainly attributed to the difference in polarity and to the lipophilic nature of their molecules relative to Clob cation. The mechanism of the selectivity is mainly based on the electrostatic environment and it is dependent on how good the fit is between the locations

Table 3
Selectivity coefficient for the Clob-electrodes in batch and FI conditions

Interferent	$-\log K^{pot}_{Clob,J^{z+}}$					
	Clob-PT			Clob-PM		
	Batch		FI	Batch		FI
	SSM	MPM		SSM	MPM	
Li^+	2.5	–	2.3	2.6	–	2.2
Na^+	2.6	–	2.0	2.3	–	2.0
K^+	2.5	–	2.0	2.5	–	2.0
Mg^{2+}	4.2	–	3.3	4.1	–	3.6
Ca^{2+}	4.0	–	3.1	4.0	–	3.4
Ba^{2+}	3.9	–	3.2	4.0	–	3.2
NH_4^+	2.6	–	2.6	2.6	–	2.9
Co^{2+}	4.0	–	4.0	4.0	–	4.2
Cu^{2+}	4.1	–	3.9	4.1	–	3.9
Mn^{2+}	4.1	–	3.9	4.1	–	4.1
Vitamin B_1	2.1	–	1.5	2.2	–	1.4
Vitamin B_6	2.5	–	1.9	2.5	–	1.8
Vitamin C	–	2.7	–	–	2.6	
Glucose	–	2.4	–	–	2.6	
Fructose	–	2.8	–	–	2.6	
Lactose	–	2.6	–	–	2.5	
Maltose	–	2.6	–	–	2.5	
Glycine	–	2.6	–	–	2.3	
Alanine	–	2.8	–	–	2.5	
Urea	–	2.8	–	–	2.3	

SSM: separate solution method; MPM: matched potential method.

of the lipophilicity sites in the two competing species in the bathing solution side and those present in the receptor of the ion exchanger [24]. Comparing the selectivity coefficient values for the investigated electrodes in batch and FI conditions, it is obvious that there is an appreciable difference. This is interpreted by difference in contact time of interferents with the membrane compared to the main sensed ion [25].

3.4. Analytical applications

The investigated electrodes were proved to be useful in the potentiometric determination of ClobCl in pure solutions and in pharmaceutical preparation (Silomat® tablets, 40 mg). The mean recovery and the relative standard deviation values are summarized in Table 4. The data indicate that there is no interference from the excipients used in the formulations of the tablets.

As the drug is not listed in any pharmacopoeia yet, the results obtained were compared with the UV first derivative published method [5] (Table 5). The results are in good agreement with those obtained from the reference method

Student's *t*- and *F*-tests (at 95% confidence level) were applied [26]. The results show that the calculated *t*- and *F*-values did not exceed the theoretical values.

The oral dosage of ClobCl for adults is 40 or 80 mg, three times daily. Clinical pharmacological studies indicated that ClobCl is rapidly absorbed after oral administration in humans. The principal route of elimination is via the urine and importantly for the present application, no known metabolite has been reported [27,28]. Recently, a HPLC method was developed for the determination of ClobCl in spiked urine samples in the concentration range (2.05×10^{-4})–(6.84×10^{-4}) M [6].

Determination of ClobCl in spiked urine samples was also carried at three different levels of concentration in batch and

Table 4
Determination of ClobCl in pure form and in pharmaceutical preparations by applying standard addition and potentiometric titration methods and under FI conditions ($n = 4$)

	Taken (M)	$(Clob)_3$-PT		$(Clob)_3$-PM	
		Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)
Pure solution					
Standard addition	8.00×10^{-5}	100.2	0.5	100.3	0.3
	2.00×10^{-4}	97.9	0.5	99.0	0.8
	5.00×10^{-4}	98.9	0.5	99.8	2
	8.00×10^{-4}	98.8	2	100.5	2
Potentiometric titration	1.80×10^{-3}	98.3	2	99.6	0.1
	2.40×10^{-3}	97.7	2	99.8	0.1
	3.00×10^{-3}	99.1	2	99.0	0.4
Pharmaceutical preparation (Silomat® tablets, 40 mg)					
Standard addition	8.00×10^{-5}	97.5	0.6	98.3	0.3
	2.00×10^{-4}	97.1	0.6	97.1	1
	5.00×10^{-4}	98.7	1	98.3	1
	8.00×10^{-4}	97.0	2	98.6	2
Potentiometric titration	1.80×10^{-3}	96.5	1	96.1	2
	2.40×10^{-3}	97.8	1	96.5	0.4
	3.00×10^{-3}	97.4	0.5	97.0	0.1
FI	1.00×10^{-4}	96.8	0.1	96.9	0.8
	3.00×10^{-4}	99.1	2	98.1	1
	5.00×10^{-4}	96.8	0.1	101.4	1

Tablet composition: clobutinol hydrochloride, 40 mg—calcium hydrogen phosphate anhydrous–lactose–povidon–amylose–magnesium stearate–talc–saccharose–acaciae gum–erythrosine–titanium dioxide–macrogol 6000–cera alba–cera carnauba.

Table 5
Statistical comparison between results of pharmaceutical preparation Silomat® tablets on applying the proposed and reference methods

Parameter	Proposed methods			Reference method [5]
	Standard addition	Potentiometric titration	FI	
$(Clob)_3$-PT				
Mean recovery	97.6	97.2	97.6	97.2
S.D.	1.036	0.877	0.569	1.18
R.S.D.	1.062	0.902	0.583	1.21
F-ratio (9.28)[a]	1.291	1.801	4.279	
t-Test (2.447)[b]	0.523	0.041	0.597	
$(Clob)_3$-PM				
Mean recovery	98.1	96.5	98.8	
S.D.	1.194	0.792	1.008	
R.S.D.	1.217	0.821	1.020	
F-ratio	1.029	2.209	1.363	
t-Test	1.085	0.916	2.090	

Average of four determinations for the proposed and reference methods.
[a] Tabulated *F*-value at 95% confidence level.
[b] Tabulated *t*-value at 95% confidence level and 6 degrees of freedom.

Table 6
Determination of clobutinol hydrochloride in spiked urine samples by applying standard addition and FI methods ($n = 4$)

	Taken (M)	$(Clob)_3$-PT		$(Clob)_3$-PM	
		Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)
Standard addition method	2×10^{-4}	98.1	1	97.1	2
	5×10^{-4}	98.7	0.9	99.6	1
	8×10^{-4}	102.2	0.9	98.0	1
FI method	3×10^{-4}	97.0	0.3	100.5	0.5
	5×10^{-4}	97.7	1.0	100.1	0.2
	1×10^{-3}	96.3	0.5	100.5	0.5

FI conditions. No special care was needed for using buffered solution given the pH undependent profile of the electrode in the pH range 4.0–8.5 (Fig. 2). The mean recoveries and relative standard deviations were calculated and summarized in Table 6. Good recoveries were obtained for both systems.

4. Conclusions

The proposed plastic membrane electrodes based on $(Clob)_3$-PT or $(Clob)_3$-PM ion exchangers as the electroactive compounds are useful sensors in batch and FI conditions for determining clobutinol hydrochloride in pure drug, pharmaceutical preparations, and spiked urine samples. The sensors offer the advantage of fast response, good selectivity, long-term stability, relatively low cost and applicability over a wide pH range with minimal sample pretreatment.

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