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Potentiometric flow injection analysis of mebeverine hydrochloride in serum and urine

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Abstract

Four PVC membrane electrodes for the determination of mebeverine hydrochloride (MvCl) were fabricated and fully characterized in terms of composition, life span, usable pH range, working concentration range and temperature. The membranes of these electrodes consist of mebeverinium-silicotungstate (Mv-ST), silicomolybdate (Mv-SM), phosphotungstate (Mv-PT), or phosphomolybdate (Mv-PM) ion-associations dispersed in PVC matrix with dibutyl phthalate plasticizer. The electrodes showed near-Nernstian response over the concentration range of 4.0×10^{-6} to 1.0×10^{-2} M MvCl and were applied to the potentiometric determination of mebeverinium ion in pharmaceutical preparations, serum and urine in steady state and flow injection (FI) conditions with average recoveries of 96.4–102 % and relative standard deviations of 0.132–1.86%. The electrodes exhibit good selectivity for MvCl with respect to a large number of inorganic cations, organic cations, sugars and amino acids. The sensitivities of these electrodes are high enough to measure as low as 1.86 μg/ml of MvCl which permit the determination of the K_{sp} values of the ion-associates used. The proposed potentiometric methods offer the advantages of simplicity, accuracy, automation feasibility and applicability to turbid and colored sample solutions.

Keywords: Mebeverine hydrochloride; Ion-selective electrode; Ion-exchanger; FI conditions; Biological fluids; PVC membrane

1. Introduction

Mebeverine (3,4-dimethoxybenzoic acid 4-[ethyl-(2-[4-methoxyphenyl]-1-methylethyl)-amino] butyl ester [2753-45-9] is an antispasmodic agent with a direct, nonspecific relaxant effect on smooth muscle [1,2]. Although it has been used clinically for treatment of irritable bowel syndrome for many years. The reported methods for the determination of mebeverine, in the main, are chromatographic which, in spite of their good sensitivities, are very expensive, time consuming and require special training. They include high performance liquid chromatography [3–6], online micellar electrokinetic chromatography [7], high-performance thin layer chromatography [8,9], supercritical-fluid chromatography–mass spectrometry [10], and online reversed-phase liquid chromatography–gas chromatography [11]. Other alternatives include, spectrophotometry [12–15] and first-derivative UV-spectrophotometry [16].

Ion-selective electrodes have found vast applications in diverse fields of analysis, being of low cost, selective, sensitive and applicable over a wide range of experimental conditions. In recent decades, many intensive studies on the design and synthesis of highly selective and sensitive ion-carriers as sensory molecules for ion-selective electrodes have been reported. In spite of successful progress in the design of highly selective electrodes for various ions, there has not been any report on the development of selective and sensitive mebeverine sensors. This work, describes the construction, performance characteristics and analytical applications of four sensors selective for mebeverine. Each of these sensors incorporates an ion-association of the mebeverinium cation (Mv^+) with silicotungstate, silicomolybdate, phosphotungstate, or phosphomolybdate anion as electroactive material in PVC matrix membrane plasticized with dibutyl phthalate.

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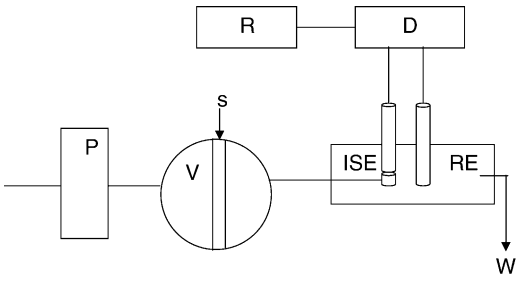

Fig. 1. FI system for Mebeverine determination; S, sample; P, peristaltic pump; V, injection valve; ISE, Mv-electrode; RE, reference electrode; D, detector; R, recorder; W, waste.

2. Experimental

2.1. Apparatus

The potentiometric measurements in steady state mode were carried out with a Jenway 3010 digital pH/mV meter. A Techne circulator thermostat Model C-100 (Cambridge, England) was used to control the temperature of the test solution. A WTW packed saturated calomel electrode (SCE) was used as an external reference electrode. The electrochemical system is represented as follows: Ag/AgCl/filling solution/membrane/test solution//SCE.

A single-stream FIA manifold (Fig. 1) was used, which is 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 micro-processor pH/ion-meter pMX 2000 (Weilheim, Germany) and interfaced to a strip chart recorder model BD111 from Kipp and Zonn (Deflt, Netherlands).

2.2. Reagents and materials

MvCl (EIPICO Tenth of Ramadan city, Cairo, Egypt). All reagents used were chemically pure grade and doubly distilled water was used throughout. Silicotungstic acid (STA), phosphotungstic acid (PTA), phosphomolybdic acid (PMA) were commercially available (Sigma). Silicomolybdic acid (SMA), poly(vinyl chloride) powder (PVC), dibutyl phthalate (DBP), dioctyl phthalate (DOP), dioctyl sebacate (DOS), tricresyl phosphate (TCP), diisononyl phthalate (DINP) and tetrahydrofuran (THF) were obtained from Aldrich chemical company. The pharmaceutical preparation containing mebeverine HCl (Colospasmin, tablets, 100.0 mg MvCl/tablet) was obtained from local drug stores.

Aqueous solutions of STA, SMA, PTA, and PMA (all in concentration of 0.01 M) were prepared from materials of analytical grade purity. The exact concentrations of these solutions were determined by the appropriate recommended methods [17,18].

Table 1
Elemental analysis of mebeverinium ion-exchangers

	Ion-exchanger	Color	%C	%H	%N	%M
Found	Mv-ST[a]	Yellow	26.17	3.07	1.21	47.87
Calculated			26.11	3.13	1.22	48.02
Found	Mv-SM[b]	Yellow	34.70	4.17	1.61	32.33
Calculated			33.90	4.07	1.58	32.53
Found	Mv-PT[c]	Buff	21.50	2.62	1.01	52.75
Calculated			21.59	2.59	1.01	52.94
Found	Mv-PM[d]	Yellow	28.90	3.52	1.40	37.12
Calculated			28.92	3.47	1.35	36.99

[a] $[C_{25}H_{36}NO_5]_4[SiW_{12}O_{40}]$.
[b] $[C_{25}H_{36}NO_5]_4[SiMo_{12}O_{40}]$.
[c] $[C_{25}H_{36}NO_5]_3[PW_{12}O_{40}]$.
[d] $[C_{25}H_{36}NO_5]_3[PMo_{12}O_{40}]$.

2.3. Preparation of the ion-exchangers

The ion-exchangers, mebeverinium-silicotungstate (Mv-ST), mebeverinium-silicomolybdate (Mv-SM), mebeverinium-phosphotungstate (Mv-PT) and mebeverinium-phosphomolybdate (Mv-PM) were prepared by adding 100 ml of 10^{-2} m MvCl hot solution to the appropriate volume of 10^{-2} m solution each of STA, SMA, PTA and PMA. The formed precipitates were filtered off, washed thoroughly with distilled water, dried at room temperature and ground to a fine powders. The chemical compositions of the precipitates were found to be [Mv_4-ST], [Mv_4-SM], [Mv_3-PT] and [Mv_3-PM] as confirmed by (C, H, N and M) elemental analysis at Cairo University Micro Analytical Center, results are given in Table 1.

2.4. Preparation of the electrodes

The membranes were prepared as previously described by Thomas and co-workers [19]. Each of the four membrane composition was studied by varying the percentage (w/w) of the ion-exchanger, PVC and plasticizer until optimum composition that exhibits the best performance characteristics is achieved. In each case, after curing, small disks (7.5 mm) were punched from the cast films and mounted in a home-made electrode bodies. The electrodes Mv-ST (electrode A), Mv-SM (electrode B), Mv-PT (electrode C) and Mv-PM (electrode D) were filled with a solution that is 10^{-1} M with respect to NaCl and 10^{-3} M MvCl and pre-conditioned by soaking in 10^{-3} M MvCl.

2.5. Potentiometric determination of MvCl

The standard additions method [20] was applied in which small increments (50–100 μL) of standard MvCl solution (10^{-1} M) were added to 50 ml aliquot samples of various concentrations from drug or sample solution equivalent to 0.466–46.6 mg MvCl in water. The change in potential at (25 ± 0.1 °C) was reported for each increment and these data

were used to calculate the concentration of MvCl in the sample solution.

2.6. Determination of MvCl in Colospasmin tablets

The contents of 10 tablets of Colospasmin (100 mg MvCl/tablet) were powdered and an accurately weighed portion equivalent to 200 mg of MvCl was mixed with 50 ml doubly distilled water, shaken in a mechanical shaker (Burrell Corp.) for a bout 24 h and filtered into a 100 ml volumetric flask. The solution was completed to the mark with doubly distilled water and shaken. Different volumes of the solution (1.0–10.0 ml) were taken and subjected to the potentiometric determination.

2.7. Determination of MvCl in biological fluids

Different quantities of MvCl and 1 ml serum or 5 ml urine, were transferred to a 100 ml volumetric flask, completed with water and small volumes (0.1–2 ml) of 0.01 M HCl to the mark to give solutions of pH ranging from 4 to 5 and concentrations of 1.0×10^{-4} to 2.8×10^{-3} M MvCl. These solutions are subjected to the potentiometric standard additions method for Mv^+ determination.

2.8. Potentiometric titration

An aliquot of MvCl, solution, containing (4.66–69.90 mg) MvCl was transferred into a 100 ml beaker, diluted to approximately 50 ml with distilled water and then titrated against standard solution of STA, SMA, PTA or PMA using any of the prepared Mv-electrodes as indicator electrode. The end points were determined from the S-shaped curve by first and second derivative plots.

2.9. Determination of the solubility product constants of the ion-exchangers

About 0.5 g portion of each ion-exchanger was added to 50 ml distilled water, the solutions were shaken for about 12 h and left to stand for a week to attain a stable equilibrium. Then, each saturated solution was decanted to a dry beaker and the equilibrium concentration of the Mv^+ ion present was determined potentiometrically using any of the fabricated electrodes by the standard additions method, and hence the solubility product constants of the ion-associates were calculated.

3. Results and discussion

3.1. Optimization of the ISE response in steady state condition

3.1.1. Electrode characteristics

Several membrane compositions were investigated for each of the studied electrodes. The plasticized PVC-based membranes containing the Mv-ST, Mv-SM, Mv-PT or Mv-PM ion-associates generated stable potential responses in solutions containing MvCl. Therefore, we studied in details the performance of the membrane electrodes based on these ion-associates as ion-exchangers for mebeverinium ion (Mv^+) in aqueous solutions.

In preliminary experiment, membranes with and without ion-exchanger were constructed. The membranes with no exchangers displayed no measurable response toward Mv^+, whereas, in the presence of the proposed ion-exchangers, the optimized membranes demonstrated Nernstian response and remarkable selectivity for Mv^+ over several common inorganic and organic cations. Thus, several membranes of varying nature and ratios of ion-exchanger/PVC/plasticizer were prepared for the systematic investigation of the membranes compositions, and the results are summarized in Table 2.

Besides the critical role of the nature and the amount of ion-exchanger in preparing membrane-selective sensors, some other important features of the PVC membrane, such as the nature of the solvent mediator, the plasticizer/PVC ratio and the nature of any additives used, are known to significantly influence the sensitivity and selectivity of ion-selective electrodes [21–23]. It should be noted that the nature of the plasticizer influences the dielectric constant of the membrane and consequently the mobility of the ion-exchanger [24,25].

The influence of the plasticizer type and concentration on the characteristics of the Mv-sensors was investigated by using five plasticizers with different polarities including DBP, DOP, DOS, TCP and DINP. Different plasticizer/PVC (w/w) ratios were studied, the 1:1 plasticizer/PVC ratio produced maximum sensitivity for all of the plasticizers. The electrodes containing DBP generally showed better potentiometric responses, i.e. sensitivity and linearity range of the calibration

Table 2
Optimization of membranes ingredients

Membrane	Composition % (w/w)			Slope (mV/decade)	R.S.D. (%)*
	Ion-associate	DBP	PVC		
Mv-ST	0.5	49.75	49.75	50.1 ± 0.4	0.99
	1	49.50	49.50	56.3 ± 0.3**	0.44
	3	48.50	48.50	53.2 ± 0.2	0.75
	5	47.50	47.50	51.7 ± 0.3	1.14
Mv-SM	0.5	49.75	49.75	59.2 ± 0.2**	0.32
	1	49.50	49.50	57.1 ± 0.3	0.25
	3	48.50	48.50	57.2 ± 0.4	0.56
	5	47.50	47.50	55.4 ± 0.2	0.89
Mv-PT	0.5	49.75	49.75	54.1 ± 0.3	1.08
	1	49.50	49.50	54.2 ± 0.2	0.72
	3	48.50	48.50	55.2 ± 0.2**	0.54
	5	47.50	47.50	55.3 ± 0.1	0.69
Mv-PM	0.5	49.75	49.75	53.4 ± 0.4	0.43
	1	49.50	49.50	56.3 ± 0.3**	0.33
	3	48.50	48.50	54.2 ± 0.1	0.85
	5	47.50	47.50	54.1 ± 0.2	0.71

* Relative standard deviation (five determinations).
** Selected composition.

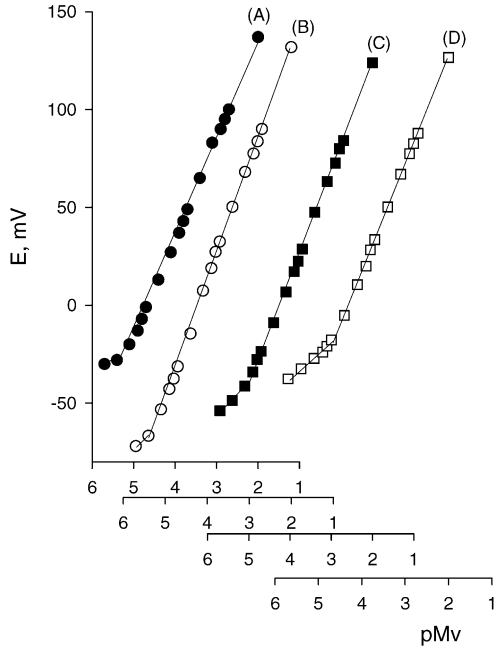

Fig. 2. Calibration graphs for electrodes (A), (B), (C) and (D) at optimum membrane composition.

plots. It seems that DBP, as a low polarity compound, provides more appropriate conditions for incorporation of the highly lipophile Mv^+ ion into the membrane prior to its exchange with the soft ion-exchanger. Therefore, we used DBP as a suitable plasticizer for further studies.

The potentiometric response of the electrodes prepared with different amounts of Mv-ST, Mv-SM, Mv-PT and Mv-PM was examined in the concentration range 1.0×10^{-6} to 1.0×10^{-1} M MvCl solutions. The calibration plots for the electrodes are shown in Fig. 2, which show linearity over the concentration range of 4.0×10^{-6} to 1.0×10^{-2} M. The lower limit of detection, defined as the concentration of MvCl corresponding to the intersection of the extrapolated linear segment of the calibration graphs, ranged between 4.0×10^{-6} and 4.0×10^{-5} M.

The response time [26] of the electrodes was tested by measuring the time required to achieve a steady state potential (within ±1 mV) after successive immersion of the electrodes in a series of MvCl solutions, each having a 10-fold increase in concentration from 1.0×10^{-5} to 1.0×10^{-2} M. The electrodes yielded steady potentials within 5–10 s. The potential reading stay constant, to within ±1 mV, for at least 5 min. Typical potential–time plot for the response of the electrode based on Mv-PM is shown in Fig. 3. The response characteristics of the electrodes which were systematically evaluated according to the IUPAC recommendations [26] are summarized in Table 3.

The repeatability of the potential reading for each electrode was examined by subsequent measurement in 1.0×10^{-3} M of MvCl solution immediately after measuring the first set of solution at 1.0×10^{-4} M of MvCl. The standard deviation of measuring emf for five replicate mea-

Table 3
Response characteristics of the Mv-electrodes

Parameter	Electrode (A)	Electrode (B)	Electrode (C)	Electrode (D)
Composition (%) (ion-associate–PVC–DBP)	1.0–49.5–49.5	0.5–49.75–49.75	3.0–48.5–48.5	1.0–49.5–49.5
Slope (mV/decade)				
Batch	56.0	59.0	55.0	56.0
FIA	80.2	76.6	82.7	78.3
Linearity range (M)				
Batch	4.0×10^{-6} to 1.0 × 10-2	4.0×10^{-6} to 1.0×10^{-2}	7.9×10^{-6} to 1.0×10^{-2}	2.0×10^{-5} to 1.0×10^{-2}
FIA	1.0×10^{-4} to 1.0×10^{-1}	1.0×10^{-4} to 1.0×10^{-1}	5.0×10^{-4} to 1.0×10^{-1}	5.0×10^{-4} to 1.0×10^{-1}
Correlation coefficient				
Batch	0.994	0.999	0.995	0.990
FIA	0.999	0.996	0.991	0.999
Detection limit (M)				
Batch	3.1×10^{-6}	4.0×10^{-6}	8.0×10^{-6}	2.0×10^{-5}
FIA	9.0×10^{-5}	1.0×10^{-4}	5.5×10^{-4}	5.3×10^{-4}
Working pH range	1.0–6.5	1.0–6.5	1.0–6.5	1.0–6.5
Response time (s)				
Batch	5–8	5–8	8–10	5–8
FIA	4–6	5–7	4–8	6–8
Life span (days)	55	50	29.0	22.0

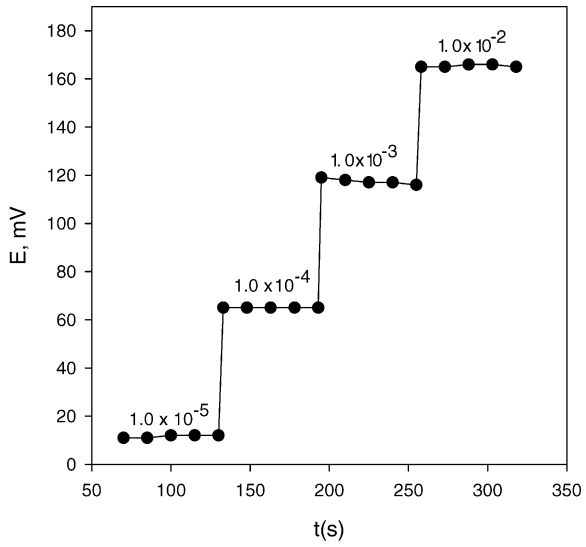

Fig. 3. Typical potential–time plot for the response of electrode (D).

surements obtained are 1.50, 0.58, 1.14, and 0.71, for electrodes A, B, C and D respectively in 1.0×10^{-4} M solution, and 1.58, 0.50, 0.89 and 0.55 in 1.0×10^{-3} M solution. This indicates the excellent repeatability of the potential response of the electrodes.

3.1.2. Effect of temperature

To study the thermal stability of the electrodes, calibration graphs [electrode potential (E_{cell}) versus pMv] were constructed at different test solution temperatures covering the range 25–55 °C. The isothermal coefficients (dE/dt) of the electrodes were calculated [27] and found to be 0.00009, 0.00008, 0.00009 and 0.00006 V/°C and E_{cell} 0.0009, 0.0007, 0.0005 and 0.0007 V/°C for electrodes A, B, C and D, respectively. These values indicate fairly high thermal stability of the electrodes within the temperature range investigated and show no deviation from the theoretical Nernstian behavior.

3.2. Optimization of FI conditions

Flow injection analysis (FIA) becomes a widespeared type of methodology characterized by its versatility, ease of automation, high sampling frequency and minimum sample treatment prior to injection into the system.

FIA parameters were optimized in order to obtain the best signal sensitivity and sampling rate under low dispersion conditions. The dispersion coefficients ranged from 1.14 to 1.50, i.e. limited dispersion that aids optimum sensitivity and fast response of the electrodes.

The influence of sample size and flow rate on the performance of the electrode response was assessed by injecting different volumes of 10^{-3} M MvCl solution, at different flow rates. The sample loop of size 500 μl and flow rate of 12.5 ml/min were found to be the optimum and used throughout this work. Fig. 4 shows the recordings (a) and the calibration graph (b) obtained for electrode (A) at optimum FIA conditions.

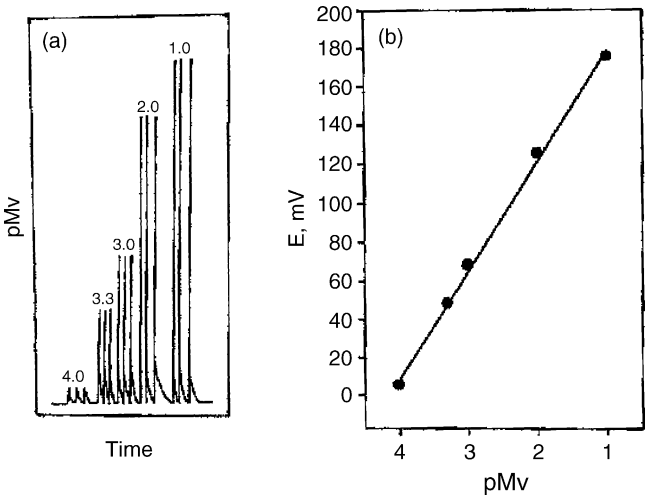

Fig. 4. Recording (a) and its corresponding calibration graph (b) obtained for calibration graph (b) obtained for electrode (A) at optimum FLA conditions.

Under the optimized FIA conditions the electrodes presented practical detection limits of 9.0×10^{-5} to 5.5×10^{-4} M which are higher than those obtained in steady state mode. The lower sensitivities of the electrodes in FIA may be attributed to many factors such as mass transport rate, the non-uniformity of concentration profile at electrode surface, the sample dispersion and the effect of contact time between the sample and the electrode [28]. In general this behavior is similar to that presented by the authors for previously described electrodes [29,30].

3.3. Effect of pH

The effect of the pH of the test solution on the electrode potentials was studied in steady state and FIA measurements. In steady state measurements, the variation in potential with pH changes from 1.0 to 11 was followed by the addition of small volumes of (0.1–1.0 M) of HCl and NaOH to different concentrations of MvCl solutions. As can be seen from the results shown in Fig. 5, the potential variation due to pH change is considered acceptable in the pH range 1.0–7.2. Nevertheless, at pH values higher than 7.2, the potential decreases gradually, which can be attributed to the formation of the free mebeverine base in the test solution.

In FIA, a series of solutions of concentration that are 10^{-2} M MvCl and have pH values ranging from 1 to 8 were injected in the flow stream, then the peak heights, representing variation of potential response with pH changes, were measured. No variation in the peak heights were observed in the pH range 1–7.2. This indicates that the electrodes do not respond to pH changes in this range under FIA conditions.

3.4. Selectivity of the electrodes

The influence of some inorganic cations, organic cations, sugars, urea and amino acids on the Mv-electrodes was investigated. In the steady state conditions, the matched potential

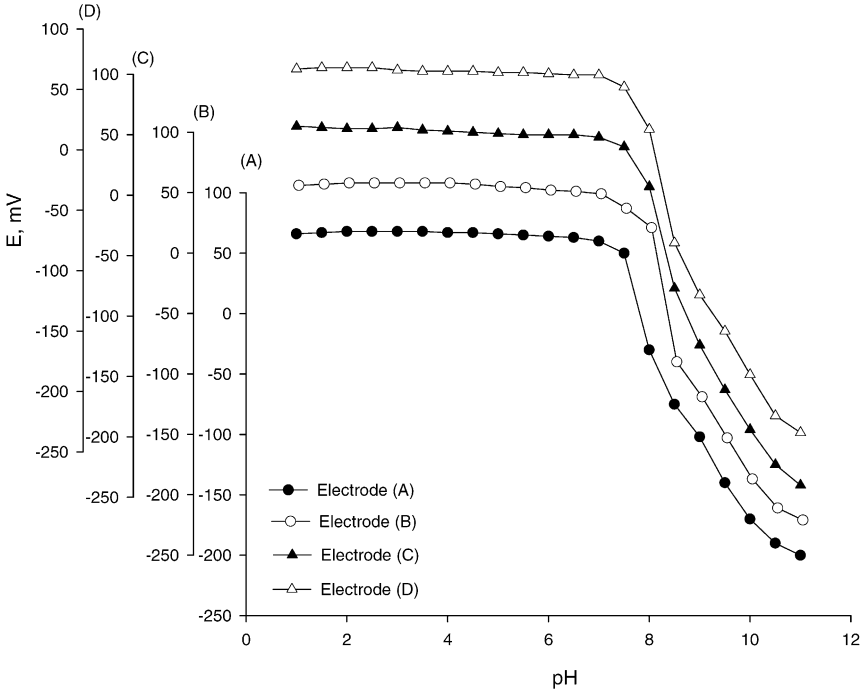

Fig. 5. Effect of pH on the potential response of electrodes (A), (B), (C) and (D) in 1.0×10^{-3} MvCl.

method was applied [31,32]. Among the different mixed solution methods, the matched potential method is unique in that it depends neither on the Nicolsky–Eisenman equation nor on any of its modifications. This method was recommended in 1995 by IUPAC as a method that gives analytically relevant practical selectivity coefficient values. To determine the selectivity coefficient of different interfering ions for Mv-electrodes, the potential of a reference solution of MvCl ($a_{Mv} = 1 \times 10^{-5}$ M) was measured and specified amounts of MvCl (a'_{Mv}) in the range of 2×10^{-4} to 5×10^{-5} M MvCl were added to the reference solution and the potential was measured and the corresponding potential change (ΔE) is recorded. In a separate experiment, the interfering ions (J) (in the range of 1.0×10^{-1} to 1.0×10^{-2} M) were successively added to an identical reference solution until the change in potential matched the ΔE value. The values of $K^{Pot}_{Mv,J^{z+}}$, are then calculated using the following equation:

$$K^{Pot}_{Mv,J^{z+}} = \frac{a'_{Mv} - a_{Mv}}{a_J}$$

where a_J is the activity of the added interferent.

In FI conditions, the values of selectivity coefficients were calculated based on potential values measured at the tops of the peaks for the same concentrations of the drug and the interferent according to the separate solution method [33], since the matched potential and other mixed solution methods, in this case are time consuming due to the needs of many solutions and perform many steps.

The selectivity coefficient values $-\log K^{Pot}_{Mv,J^{z+}}$ of the electrodes listed in Table 4 reflect a very high selectivity of these electrodes for mebeverinium cation.

The mechanism of selectivity is mainly based on the stereospecificity and electrostatic environment and it is dependent on how much fitting is present between the locations of the lipophilicity sites in the two competing species in the bathing solution side and those present in the receptor of the ion-exchanger [34]. Inorganic cations do not interfere because of differences in ionic size, mobility and permeability. The electrodes are also selective to Mv^+ over number of sugars, amino acids, and organic cations namely thiamine and pyridoxine hydrochlorides. The performance of the electrodes was examined in presence of different anions including chloride, nitrate, sulphate, phosphate, thiocyanate, acetate and citrate. No effect was observed from these anions except citrate and sulphate. However, these are not present in the formulations. For this reason, they do not prejudice the quality of the determinations.

3.5. Solubility products of the ion-exchangers

Pungor and Toth [35] have shown that the solubility products of the precipitates constituting the ion-selective membranes determine the detection limits of precipitate-based electrodes. The high sensitivities of the present electrodes which are enough in some cases to measure as low as 1.86 μg/ml of MvCl enabled us to use them in the determination of the solubility of the studied ion-exchangers and hence to calculate their solubility products. The solubility product constants (K_{sp}) of Mv_4-ST, Mv_4-SM, Mv_3-PT and Mv_3-PM at 25 °C were calculated and found to be 6.0×10^{-31}, 3.5×10^{-30}, 1.0×10^{-22} and 9.1×10^{-20} respectively. To affirm the validity of this method, the K_{sp} values of these

Table 4
Selectivity coefficient $-\log K^{Pot}_{Mv,J^{z+}}$ for Mv-electrodes

Interfering ions	Electrode (A)		Electrode (B)		Electrode (C)		Electrode (D)	
	Batch	FIA	Batch	FIA	Batch	FIA	Batch	FIA
Na^+	3.44	2.21	3.21	2.47	3.87	2.00	3.09	1.94
NH_4^+	3.80	2.32	3.08	2.56	3.66	2.09	3.21	2.04
K^+	3.58	2.21	3.23	2.57	3.91	2.11	3.33	2.04
Ca^{2+}	4.22	3.04	4.24	3.36	4.11	2.97	4.08	2.91
Zn^{2+}	4.12	3.21	4.20	3.47	4.09	3.11	3.87	3.03
Ni^{2+}	4.07	3.06	4.02	3.31	4.15	3.08	3.98	2.80
Ba^{2+}	4.16	3.29	4.34	3.35	4.12	2.89	4.09	2.88
Mg^{2+}	4.22	2.98	4.23	3.43	4.33	2.95	4.00	2.91
Mn^{2+}	4.11	3.00	4.21	3.21	4.21	2.75	4.12	2.77
Pb^{2+}	4.13	3.04	4.27	3.12	4.17	3.00	4.11	2.89
Hg^{2+}	4.24	3.19	4.33	3.41	4.32	3.13	4.21	2.97
Cd^{2+}	4.10	2.95	4.38	3.25	4.10	3.01	4.07	2.86
Cu^{2+}	4.05	2.92	4.00	3.31	4.22	2.93	4.23	2.82
Sr^{2+}	4.07	3.06	4.45	3.41	4.06	3.00	3.97	2.82
Cr^{3+}	4.17	3.54	4.00	3.81	4.08	3.42	4.21	3.37
Al^{3+}	4.23	3.44	4.53	3.64	4.23	3.32	4.00	3.34
Thiamine H^+Cl^-	4.25	3.55	3.02	2.85	4.11	3.15	4.32	3.14
Pyridoxine H^+Cl^-	4.22	3.54	3.88	3.08	4.09	3.33	4.21	3.18
Glucose	4.23	–	4.35		4.34	–	3.21	
Fructose	4.21	–	4.33		4.20	–	4.21	
Lactose	4.12	–	4.32		4.21	–	3.21	
Maltose	4.31	–	4.22		4.32	–	4.00	
Vitamin C	3.02	–	4.00		4.23	–	3.22	
Urea	3.67	–	3.87		4.21	–	4.32	
Alanine	3.52	–	4.12		3.55		3.87	
Valine	4.18	–	3.67		4.29	–	3.02	
Leucine	3.00	–	3.34		4.34	–	3.21	
Asparagine	3.43	–	3.00	–	3.26	–	3.43	–
L-Cystine	4.34	–	2.86	–	3.78	–	3.21	–
DL-Serine	4.23	–	4.34	–	4.21	–	4.21	–

compounds were calculated depending on the conductemetric method [30] and found to be 1.8×10^{-30}, 5.7×10^{-30}, 2.4×10^{-23} and 1.3×10^{-19} for Mv_4-ST, Mv_4-SM, Mv_3-PT and Mv_3-PM, respectively. It is noteworthy to mention that the solubility of an ion-exchanger is one of the main factors controlling the life span of the sensor which incorporate this ion-exchanger as electroactive material. This is confirmed by the values of solubility obtained, where the ion-exchanger of the least solubility (Mv_4-ST, of $S = 2.88 \times 10^{-7}$) has the longest life span and the lowest detection limit between the four electrodes (Table 3), while that of the highest solubility (Mv_3-PM, of $S = 7.62 \times 10^{-6}$) has the lowest useful lifetime.

3.6. Analytical applications

In order to assess the applicability of the proposed selective electrodes, the methods were applied for determination of mebeverine in its pharmaceutical preparations and in different real biological fluids such as serum and urine in both steady state and FI conditions.

The MvCl content in its pharmaceutical preparation (Colospasmin tablets) was determined by potentiometric titration against standard solution of STA, SMA, PTA or PMA. The ingredients in the tablets did not interfere with the experiments. Best results were obtained with electrodes (A) and (D) as indicated by the emf jumps at the vicinity of the end points amounting to 100–120 mV in case of titrating 4.66 mg MvCl and increase gradually as the titrated amounts of MvCl increase reaching to 220–240 mV on titrating 46.6 mg MvCl, which reflects a very high degree of completeness of the titration reaction. Fig. 6 shows typical potentiometric curves of titrating 4.66 mg MvCl using electrode (D).

Clinical pharmacological studies indicates that about 95% of orally administered mebeverine in humans is metabolized via five partially overlapping pathways [36], and about 2–5% of the dose reaches to urine. A simple method was required to determine mebeverine in these fluids following its administration at normal therapeutic dose levels to humans subjects in order to carry out bioavailability studies on different dose forms of mebeverine. Accordingly we presented this method for determination of MvCl in serum and urine samples spiked with known amounts of MvCl. The standard additions method was applied for the determinations in these real samples to overcome the matrix effects.

With the FI system, different samples were analyzed including biological fluids spiked with known amounts of MvCl

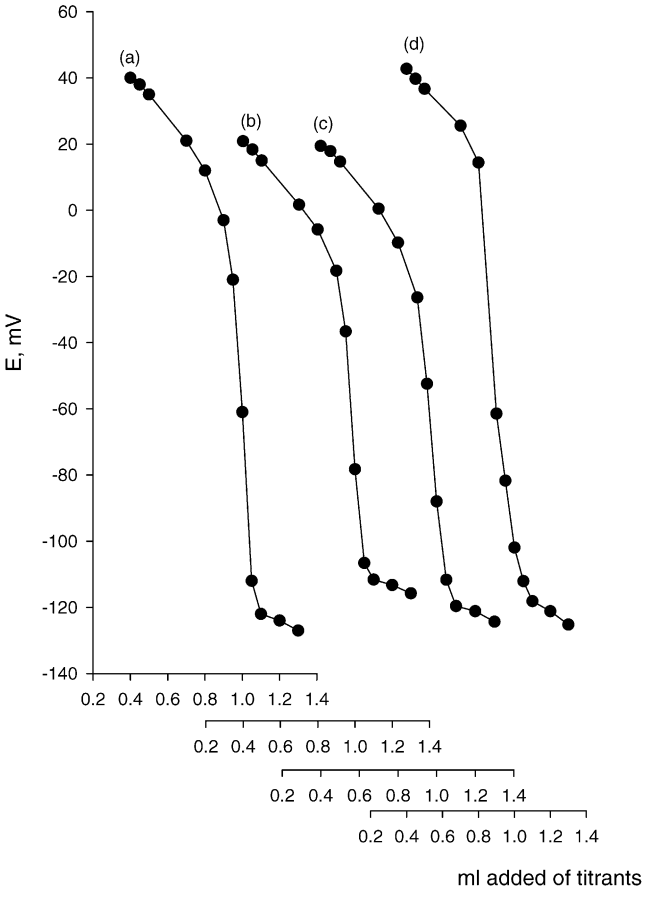

Fig. 6. Curves of the potentiometric titration of 4.66 mg MvCl with STA (a), SMA (b), PTA (c) and PMA (d) as titrants using electrode (D).

and the drug tablets. The peak height were measured, and then compared to those obtained from injecting standard solution from pure MvCl. Table 5 gives the obtained values for the previously mentioned determinations

3.7. Statistical treatment of results

The results obtained from the potentiometric determinations of the drug in steady state and in FI conditions were subjected to linear regression analysis (found values versus taken), in order to establish weather the investigated electrodes exhibit any fixed or proportional bias. The slopes and intercepts of the regression lines did not differ significantly from the ideal values revealing the absence of a systematic error during the measurements within the investigated concentration range. Also the values were compared with the results obtained from the official method [37] based on spectrophotometric determination of MvCl by applying *F*-tests [38]. The values obtained, Table 6, show that the present method is of comparable precision to that of the official method and there is no significant difference between the mean values obtained by both methods.

Table 5
Results for determination of MvCl in tablets and biological fluids using electrode (D)

Sample	Mv (mg)[b]	Recovery (%)	R.S.D. (%)[a]	Standard error	Confidence limit (99%)
Tablet					
Batch	0.978	99.48	0.925	0.005	0.055
	4.890	100.10	0.306	0.008	0.086
	9.780	101.40	0.541	0.145	1.420
FIA	0.978	97.9	0.26	0.001	0.014
	4.890	96.9	0.63	0.017	0.169
	9.780	96.6	1.58	0.086	0.847
Serum					
Batch	2.33	99.00	1.10	0.018	0.182
	4.66	101.0	0.30	0.012	0.117
	23.3	99.00	0.74	0.115	1.129
	46.6	98.00	0.55	0.174	1.700
FIA	2.33	97.1	0.24	0.003	0.036
	4.66	98.3	1.60	0.049	0.486
	23.3	96.9	0.38	0.058	0.572
Urine					
Batch	2.33	102.0	1.64	0.026	0.256
	4.66	100.0	1.39	0.044	0.432
	9.32	100.0	1.81	0.495	1.129
	23.3	101.6	0.72	0.110	1.125
	46.6	98.00	1.12	0.340	3.380
FIA	2.33	97.8	0.75	0.011	0.113
	9.32	98.3	1.86	0.115	1.13
	46.6	97.7	0.57	0.176	1.72

[a] Average of five determinations.
[b] Milligrams taken of MvCl in tablets or spiked to serum and urine samples.

Table 6
Statistical treatment of data obtained for the determination of MvCl using Mv-electrodes employing the standard additions method, the potentiometric titration and FIA in comparison with the official method

Method	$X \pm$ S.E.	Relative error (%)	$F^{3,3}$ value (9.28)
Official method	98.40 ± 0.32	1.60	
Electrode (A)			
Method (I)	101.8 ± 0.13	1.80	0.20
Method (II)	100.3 ± 0.66	0.30	4.29
Method (III)	99.30 ± 0.57	0.70	1.08
Electrode (B)			
Method (I)	101.0 ± 0.0.5	1.00	0.81
Method (II)	98.60 ± 0.30	1.40	0.90
Method (III)	96.60 ± 0.44	3.40	1.89
Electrode (C)			
Method (I)	100.1 ± 0.17	0.10	0.10
Method (II)	99.73 ± 0.86	0.27	7.31
Method (III)	96.63 ± 0.77	3.37	1.96
Electrode (D)			
Method (I)	100.8 ± 0.76	0.80	1.89
Method (II)	98.60 ± 0.47	1.40	2.13
Method (III)	98.50 ± 0.76	1.50	5.65

Method (I): standard addition method; Method (II): potentiometric titration; Method (III): FIA.

4. Conclusions

The proposed PVC-electrodes based on Mv-ST, Mv-SM, Mv-PT or Mv-PM ion-exchangers as the electroactive compounds might be useful detectors in steady state and FI systems and interesting alternatives for the determination of [Mv^+] in different real samples. The present electrodes show high sensitivity, reasonable selectivity, a fast static response, long-term stability and applicability over a wide pH range with minimal sample pretreatment. The reported methods of determination with the prescribed electrodes are simple, sensitive, highly specific and advantageous over the previously described procedures for MvCl determinations, since the interference of the recipients, impurities, degradation product or other accompanying drugs is nullified.

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