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A comparative study of solid and liquid inner contact benzalkonium chloride ion-selective electrode membranes

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ABSTRACT

A comparative study was made between two designs of benzalkonium ion (Bz)-selective electrodes: a silver-coated (solid contact) called electrode A and a PVC membrane (liquid inner contact) called electrode B based on benzalkonium-phosphomolybdate (Bz-PM) as ion-exchanger complex. Electrode A has a linear dynamic range from 2.0×10^{-8} to 1.0×10^{-2} mol L^{-1}, with a Nernstian slope of 60 ± 0.3 mV/decade and a detection limit of 2.0×10^{-8} mol L^{-1}. Electrode B shows linearity over the concentration range from 2.0×10^{-7} to 1.0×10^{-2} mol L^{-1}, with a Nernstian slope of 55 ± 1.2 mV/decade and a limit of detection of 1.5×10^{-7} mol L^{-1}. Electrode A showed better performance than electrode B. The detection limit of benzalkonium chloride (BzCl) was effectively improved by a solid contact ion-selective electrode (SC-ISE), rather than the traditional liquid inner contact electrode that gives lower detection limits because of diminished ion fluxes. The present electrodes show clear discrimination of BzCl from several inorganic, organic ions, sugars and some common drug excipients. The sensors were applied efficiently for determination of BzCl in its pharmaceutical preparations (eye, ear and nasal drops) using standard addition and the calibration curve methods.

1. Introduction

Design of electrodes with improved characteristics of a certain chemical species is a perpetual impetus in chemical research. To this end we are undertaking this work that involves the design, study and comparison of new electrodes to determine benzalkonium chloride ion in solutions. The construction of a polymeric membrane ion-selective electrode traditionally required a relatively high concentration of the ion of interest in the inner filling solution (IFS); however, experimental evidence suggested that this has a deteriorating influence on the detection limit [1]. Mathison et al. [2] showed that an increased concentration of the primary ion in the inner solution leads to its extraction from there together with its counterions forming ion fluxes from the membrane to the sample. This process changes the ion activity at the phase boundary thus significantly worsening the detection limit. One strategy to counteract this behavior is elimination of the inner solution by using a solid inner contact. In solid-contact SC-ISEs, the sensing membrane is sandwiched between the sample solution and a SC-ISEs. In recent years, therefore, research has intensified to develop solid contact electrodes with low LODs [3]. To shed light on this concept we have designed two new, a PVC and a silver-coated, benzalkonium electrodes and made a comparative study on their detection limits, concentration ranges and the effect of the internal solution on the results.

Benzalkonium chloride (BzCl) (Fig.1), is widely used as antimicrobial agent for its antiseptic and disinfectant effects depending on concentration. Its use as a preservative in cosmetics as well as in eye, air and nasal drops attests to its general safety [4]. Several analytical techniques have been used to determine benzalkonium chloride in pharmaceutical products including capillary electrophoresis [5,6], voltammetry [7], gas chromatography with flame ionization detection [8] and high performance liquid chromatography with UV detection (HPLC-UV) [9–11]. However, most of these methods comprise sample manipulations, extraction operations and derivatization reactions that are liable to various interferences as well as being not applicable to colored and turbid solutions. These methods are expensive for they require large infrastructure backup and qualified personnel. Thus, there is a critical need for the development of selective and inexpensive diagnostic tool for the determination of this analyte. Analytical methods based on potentiometric detection with ion-selective electrodes (ISEs) can be considered good alternatives for their attractable characteristics such as simple design, ease of construction, reasonable selectivity, fast response time, applicability to colored and turbid solutions providing possible interfacing with automated and computerized systems.

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Careful review of the literature spotted no solid or liquid inner contact ion-selective electrode membranes for determination of benzalkonium ion and prompted exploration to design new types of electrodes for this purpose in continuation to our work on benzalkonium analysis [12]. In this work, two new benzalkonium electrodes, namely a PVC membrane and a coated silver wire, were fabricated, optimized and checked at different concentration ranges of benzalkonium ion. The results, presented in this paper, revealed that the solid contact electrode surpass the PVC electrode. Indeed, these results are similar to those reported [13,14]. This electrode is a new example of the common behavior of the solid contact electrodes over the liquid contact ones.

2. Experimental

2.1. Reagents

Alkyl dimethyl benzyl ammonium chloride (benzalkonium chloride 50%) was obtained from Sigma-Aldrich. Graphite powder, dioctyl phthalate (DOP), dibutyl phthalate (DBP), tris(2-ethylhexyl) phosphate (TOPh) and dioctyl sebacate (DOS) as well as metal salts were purchased from Aldrich and used as received. Phosphotungstic acid (PTA) and phosphomolybdic acid (PMA) were obtained from Sigma. The pharmaceutical preparations containing BzCl, Fml (eye drop), Oflox (eye drop), Dextrol (ear drop)) and Lies (Nasal drop) are produced by Pharaonia Pharmaceuticals Co., Egypt, Otrivin baby (Nasal drop) by Novartis Co., Switzerland, Isopto-Maxidex (Eye drop) by Alcon-Couvereur Co., Belgium and DAC (liquid detergent) by Henkel PDC, Egypt.

2.2. Apparatus

Potentiometric and pH measurements were made with a Pocket pH/mV Meters, pH315i (Wissenschaftlich-Technische Werkstatten GmbH (WTW), Weilheim, Germany). The saturated calomel electrode (SCE) was used as reference electrode for potential measurements. It was obtained from Sigma-Aldrich Co. (St Louis, MO, USA). The emf measurements with silver wire and PVC membrane electrodes were carried out with the following cell assemblies:

Silver wire | PVC membrane | sample solution‖ Hg, Hg_2Cl_2(s), KCl(sat.)

Ag–AgCl ‖ internal solution 10^{-2} mol L^{-1} KCl and 10^{-3} mol L^{-1} BzCl ‖ PVC membrane ‖ sample solution ‖ Hg, Hg_2Cl_2(s), KCl(sat.)

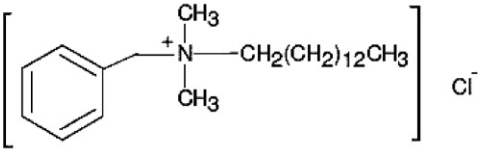


Fig. 1. Chemical structure of benzalkonium chloride (BzCl).

2.3. Preparation of ion-exchanger complex

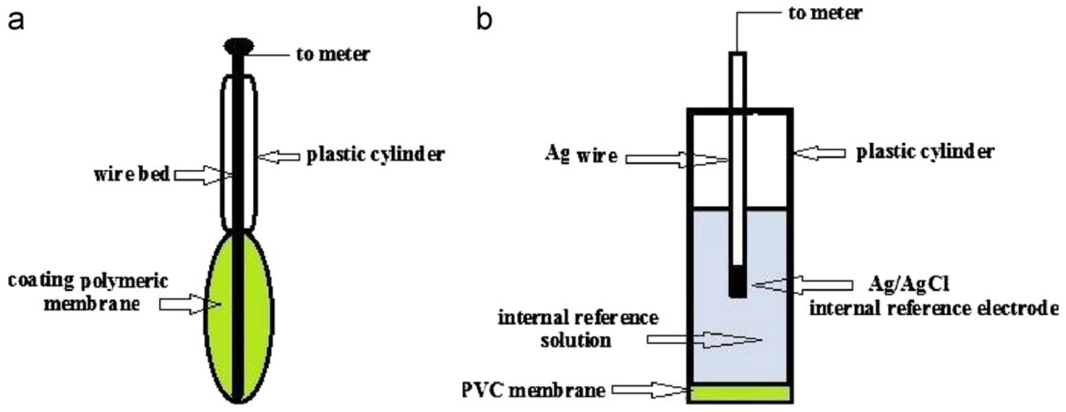
The ion-exchanger complexes benzalkonium–phosphomolybdate (Bz-PM) and benzalkonium–phosphotungstate (Bz-PT) were prepared by adding a hot solution of 50.0 mL of 0.01 mol L^{-1} BzCl to 16.7 mL of 0.01 mol L^{-1} of phosphomolybdic acid (PMA) or phosphotungstic acid (PTA) [12]. The precipitates that formed were filtered off, washed thoroughly with distilled water, dried at room temperature and ground to fine powders. These ion-exchanger complexes were used as the active substances for preparing the PVC membrane and coated wire electrodes of benzalkonium chloride.

2.4. Preparation of PVC membrane electrode

PVC-membranes were prepared as previously described elsewhere [15,16]. The membranes were prepared by dissolving optimized amounts of PVC, different plasticizers and ion-exchangers in 10 mL of tetrahydrofuran (THF). The mixture was shaken vigorously and the clear solution was poured into a glass dish 7 cm in diameter. The solvent was allowed to evaporate overnight leaving a homogeneous flexible and transparent membrane. Small disks (10 mm) were punched from the cast films and mounted on home-made electrode bodies. The electrodes were filled with the internal filling solution (0.01 mol L^{-1} KCl and 0.001 mol L^{-1} BzCl) and preconditioned by soaking for 15 min in 0.01 mol L^{-1} BzCl solution. The electrode produced is shown in Scheme 1(a).

2.5. Preparation of the coated-wire electrodes

The coated-wire electrodes (CWEs) were prepared according to a previously reported method [17,18]. Certain amounts of PVC, the ion-exchanger and one of a few selected plasticizers were dissolved in about 10 mL of THF. A silver wire about 1 mm diameter and 50 mm length was first polished on a cloth pad and washed with acetone. One end of the wire was then coated by repeated dipping into the membrane solution in THF. A membrane was formed on the wire surface and was allowed to dry overnight. The prepared electrodes were finally conditioned by soaking for 15 min in 0.01 mol L^{-1} of BzCl solution. The coated electrode produced is shown in Scheme 1(b).



Scheme 1. Schematic diagram of (a) solid and (b) liquid inner contact ion-selective electrode membranes.

2.6. Selectivity coefficient determination

Potentiometric selectivity factors of the electrodes were evaluated by applying the matched potential method (MPM) and the separate solution method (SSM) [19]. According to the MPM, the activity of (Bz^+) was increased from $\acute{a}_A = 1.0 \times 10^{-5}$ mol L^{-1} (reference solution) to $a'_A = 5.0 \times 10^{-5}$ mol L^{-1} and the change in potential (ΔE) corresponding to this increase was measured. Next a solution of an interfering ion of concentration a_b in the range from 1.0×10^{-1} to 1.0×10^{-2} mol L^{-1} is added to a fresh 1.0×10^{-5} mol L^{-1} solution (reference) until the same potential change (ΔE) was recorded. The selectivity factor, $K^{pot}_{A,b}$, for each interferent was calculated using the Eq. (1)

$$K^{pot}_{A,b} = \frac{a'_A - a_A}{a_b} \tag{1}$$

In the SSM, the potential of a cell comprising a working electrode and a reference electrode is measured in two separate solutions, one containing Bz^+ ions, E_1, and the other containing the interfering ions (J), E_2. These values were used to calculate the selectivity coefficient from the following equation:

$$K^{Pot}_{Bz^+,\, J^{z+}} = \frac{E_2 - E_1}{S} + \log[Bz^+] - \log[J^{z+}]^{1/z} \tag{2}$$

where, S is the slope of the calibration graph.

2.7. Determination of Bz^+ in pure solution and its pharmaceutical formulations

2.7.1. Standard addition method

The standard addition method in which small increments (10–100 μL) of 0.01 mol L^{-1} BzCl solution were added to 50.0 mL aliquot samples of various concentrations (1.0×10^{-6} to 3.0×10^{-5} mol L^{-1}) BzCl was applied. The potential after each increment was recorded and used to calculate the concentration of BzCl in its pharmaceutical preparations.

2.7.2. Calibration graph method

In which different amounts of BzCl were added to 50.0 mL of water comprising a concentration range from 1.0×10^{-7} to 1.0×10^{-3} mol L^{-1} and the measured potential was recorded using the present electrodes. The data were plotted as potential versus pBz^+ activity and the resulting graph was used for subsequent determination of unknown Bz^+ concentration.

2.7.3. Potentiometric titration method

Different volumes of 1.0×10^{-3} mol L^{-1} and 1.0×10^{-2} mol L^{-1} BzCl solution equivalent to 1.79–35.85 mg were transferred to a 25.0 mL beaker and titrated with a standard solution of sodium tetraphenylborate (Na-TPB) using electrodes A and B as indicators. The end points were determined from the S-shaped curves.

Table 1
Optimization of membrane ingredients and their performance characteristics of Bz-electrodes.

Composition (%)				Electrode characteristics				
No.	I.E	PVC	P (TOPh)	S	C.R (mol L^{-1})	LOD (mol L^{-1})	R.S.D	R(s)
Electrode A								
	Bz-PM							
1.	–	51.8	48.2	47 ± 1.1	5.9×10^{-6} –1.0×10^{-2}	3.2×10^{-6}	1.06	12–15
2.	0.5	51.0	48.5	49 ± 0.2	1.0×10^{-7} –1.0×10^{-2}	8.8×10^{-8}	0.24	6–8
3.	1.0[a]	50.8	48.2	60 ± 0.3	2.0×10^{-8} –1.0×10^{-2}	2.0×10^{-8}	1.50	6–8
4.	1.5	50.2	47.8	52 ± 0.7	1.9×10^{-7}–1.0×10^{-2}	9.2×10^{-8}	1.06	12–15
	Bz-PT							
5.	0.5	51.0	48.5	40 ± 0.8	7.5×10^{-7}–1.0×10^{-2}	5.2×10^{-7}	1.34	10–15
6.	1.0	50.8	48.2	48 ± 0.3	5.5×10^{-7}–1.0×10^{-2}	3.2×10^{-7}	1.02	10–12
7.	1.5	50.2	47.8	48 ± 1.1	8.4×10^{-7}–1.0×10^{-2}	4.2×10^{-7}	0.47	12–15
Effect of electrode bed using 1.0(%) Bz-PM								
8.	Platinum	50.8	48.2	43 ± 0.4	1.5×10^{-7}–1.0×10^{-2}	1.1×10^{-7}	0.24	12–15
9.	Aluminum	50.8	48.2	48 ± 0.3	5.1×10^{-6}–1.0×10^{-2}	2.0×10^{-6}	1.15	15–20
10.	Copper	50.8	48.2	44 ± 1.0	8.5×10^{-8}–1.0×10^{-2}	4.1×10^{-8}	0.41	8–10
11.	Graphite	50.8	48.2	48 ± 0.3	1.6×10^{-7}–1.0×10^{-2}	8.2×10^{-8}	0.65	15–20
Electrode B								
	Bz-PM		(DBP)					
12.	–	51.8	48.2	40 ± 0.3	3.8×10^{-5}–8.0×10^{-2}	1.1×10^{-5}	1.89	30
13.	0.5	51.0	48.5	44 ± 1.8	7.7×10^{-7}–1.0×10^{-2}	3.2×10^{-7}	0.89	15
14.	1.0	50.8	48.2	50 ± 1.1	4.3×10^{-7}–1.0×10^{-2}	2.8×10^{-7}	0.97	15
15.	1.5	50.2	47.8	45 ± 0.8	3.7×10^{-7}–1.0×10^{-2}	2.2×10^{-7}	1.02	15
16.	1.0[a]	50.8	48.1 & 0.1[b]	55 ± 1.2	2.0×10^{-7}–1.0×10^{-2}	1.8×10^{-7}	0.57	5
	Bz-PT							
17.	0.5	51.0	48.5	43 ± 1.2	9.5×10^{-6}–5.0×10^{-2}	5.1×10^{-6}	1.25	8–10
18.	1.0	50.8	48.2	50 ± 0.8	5.8×10^{-6}–1.0×10^{-2}	1.9×10^{-6}	1.32	10–15
19.	1.5	50.2	47.8	48 ± 0.8	8.8×10^{-6}–1.0×10^{-2}	4.3×10^{-6}	1.89	10–15
20.	1.0	50.8	48.1 & 0.1[b]	53 ± 0.5	7.2×10^{-7}–1.0×10^{-2}	5.0×10^{-7}	0.87	8–10

I.E: Ion-exchanger, PVC: poly vinyl chloride, P: plasticizer, S: slope (mV/decade), C.R.: concentration range, LOD: limit of detection, R(s): response time(s).

[a] Selected composition.

[b] lipophilic additive (sodium tetraphenyl borate).

2.7.4. Determination of BzCl in pharmaceutical formulations

5.0 mL of Fml (eye drop), Oflox (eye drop), Lyse (Nasal drop), Otrivin baby (Nasal drop), Isopto-Maxidex (Eye drop), Dextrol (ear drop), and DAC (liquid detergent) contain 0.04, 0.05, 0.2, 0.01, 0.1, 0.04, and 50 mg of BzCl respectively. These solutions that contain from 1.12×10^{-4} to 1.4×10^{-1} mol L^{-1} of BzCl were transferred to 25.0 mL volumetric flask to prepare from 1.0×10^{-6} mol L^{-1} to 1.0×10^{-5} mol L^{-1} and subjected to the standard addition method and calibration curve.

3. Result and discussion

Design and development of new electrodes to measure various chemical species such as benzalkonium chloride is a prospering area of research. It is rewarding to get new fabricated electrodes with competitive properties. One has to utilize the properties of the composite materials as efficiently as possible to achieve this goal. With these points in mind, we have intimately worked in the design and characterization of these electrodes: a PVC and a silver-coated wire electrode of benzalkonium chloride then compared their properties in light of these considerations.

3.1. Composition of the electrodes

It is well known that the performance characteristics of IESs based on ion-exchangers depend to a large extent on the nature of these ion-exchangers and their lipophilicities [20], the type of solvent mediator [21] and any additives used [22]. Therefore, the influences of membrane composition, nature and amount of solvent mediator as well as the amount of additives, such as sodium tetraphenylborate, on the potential response of the proposed sensors were tested and the obtained results are given in Table 1.

3.1.1. Ion-exchanger selection

Ion-exchanger complexes used in ion-selective membrane sensors should have rapid exchange kinetics and adequate stability. In addition, they should have appreciable solubility in the membrane matrix and sufficient lipophilicity to prevent leaching from the membrane into the sample solution [23,24]. The ion-exchanger incorporated in each electrode presented here was an ion-association complex of the surfactant cation with phosphomolybdic acid $H_3PMo_{12}O_{40}$ or phosphotungstic acid $H_3PW_{12}O_{40}$. These species, with high molecular weight anions: 1825 and 2880 g/mol respectively, have different lipophilicities and stabilities. They were used as electroactive materials in PVC membrane and silver coated electrodes. A few membranes with miscellaneous compositions were made and tested. From the results given in Table 1, one can see that the electrodes containing zero percent ion-exchanger complexes (sensors # 1 and 12) have lower sensitivity and selectivity with poor repeatability towards Bz cations. However, in the presence of the ion-exchanger complexes the sensor displayed remarkable selectivity for Bz cations. The solubility product of the ion-exchangers is one of the main factors controlling the sensitivity of the ion-selective electrodes. The solubility products of the Bz-PM ion-exchanger is less than Bz-PT. Therefore, the membrane containing the Bz-PM complex produced the best response (sensors # 3 and 16). Derivatives of PM ion with several chemical species are known to have lower solubility products as compared to those of PT ion [25]. It is accepted that low solubility product of a substance indicates the substance has low solubility in the medium. This is considered a favorable factor in its selection as an active ion-exchanger in the electrode and explains the slightly better response obtained when Bz-PM is utilized as the ion-exchanger. However, Bz-PT has a higher molecular weight than Bz-PM. Considering only the molecular weight one expects that Bz-PT to have lower solubility than Bz-PM. Solubility is affected by other more important factors such as polarity which has a dominant effect. The net effect is that Bz-PM has a lower solubility and thus was chosen as the active ion-pair utilized in the present electrodes. However, due to a limited solubility of the ion-exchanger in THF, membranes containing 0.5%, 1.0%, 1.5% of the ion exchangers were prepared and tested for electrode A and B. The results indicate that the best sensitivity and linear range is attained at 1.0 wt% of the ion-exchanger for sensor A and for sensor B as shown in Table 1. Further addition of the ion-exchanger hampered the results, most probably due to some inhomogeneities and possible saturation of the membrane [26].

3.1.2. The influence of anionic additives

Additives such as lipophilic anions reduce ohmic resistance and improve response behavior and selectivity in cation-selective electrodes. In addition, they enhance the selectivity of the membrane electrode in cases where the extraction capability of the ion-exchanger is poor. Furthermore, the lipophilic additive may catalyze the exchange kinetics at the sample-electrode interface [27,28]. Comparison of the data (for electrode B # 14 and 16) revealed that the sensitivity of the sensor increased and the slope of the calibration curve increased from 50 ± 1.1 to 55 ± 1.2 mV/decade with the addition of a trace of Na-TPB (about 0.1 wt%). Clearly this additive contributed significantly to the dielectric constant of the membrane in addition to the effect of the plasticizer.

3.1.3. Solvent mediators (plasticizers) effect

The solvent mediator, in particular, has a dual function: it acts as a liquifying agent, making the membrane material workable, that is enabling homogenous solubilization and modifying the distribution constant of the ion-exchanger used and sustaining these characteristics on continued use. The proportion of solvent mediator must be optimized in order to minimize the electrical asymmetry of the membrane in order to keep the sensor as clean as possible and to stop leaching to the aqueous phase [29]. For a plasticizer to be adequate for use in sensors, it should gather certain properties and characteristics such as having high lipophilicity, high molecular weight, low tendency for exudation from the membrane matrix, low vapor pressure and high capacity to dissolve the substrate and other additives present in the membrane [30]. To spot a suitable plasticizer for constructing this electrode, we tested four plasticizers, with a range of characteristics, namely: the values of dielectric constants, lipophilicity and molecular weight respectively are in parentheses, for DOP (ε_r=5.1, P_{TLC}=7.1, M.wt.=390), DBP (ε_r=6.4, P_{TLC}=4.5, M.wt.=278), DOS (ε_r=4.2, P_{TLC}=10.1, M.wt.=426) and TOPh (ε_r=4.8, P_{TLC}=10.2, M.wt.=435). TOPh and DBP as solvent mediators produced the best results for electrode A and electrode B respectively, as shown in Fig. 2. It is not clear why these mediators were the best among those used, but one can say that the outcome of their properties were the most effective on the electrode response. It is likely that increasing the lipophilicity of the ion-exchanger increases its solubility in the membrane and the electrode potential as well. However, the higher the molecular weight of the plasticizer the less soluble the ion-exchanger in the membrane. We are in front of a situation where two opposing factors are in effect and what we see is the outcome of both of these factors that produce similar effect on utilizing these plasticizers. Among the different compositions studied, the electrode containing ion-exchanger complex 1.0 wt% Bz-PM, 50.8 wt% PVC and 48.2 wt% TOPh for electrode A and 1.0 wt% Bz-PM,

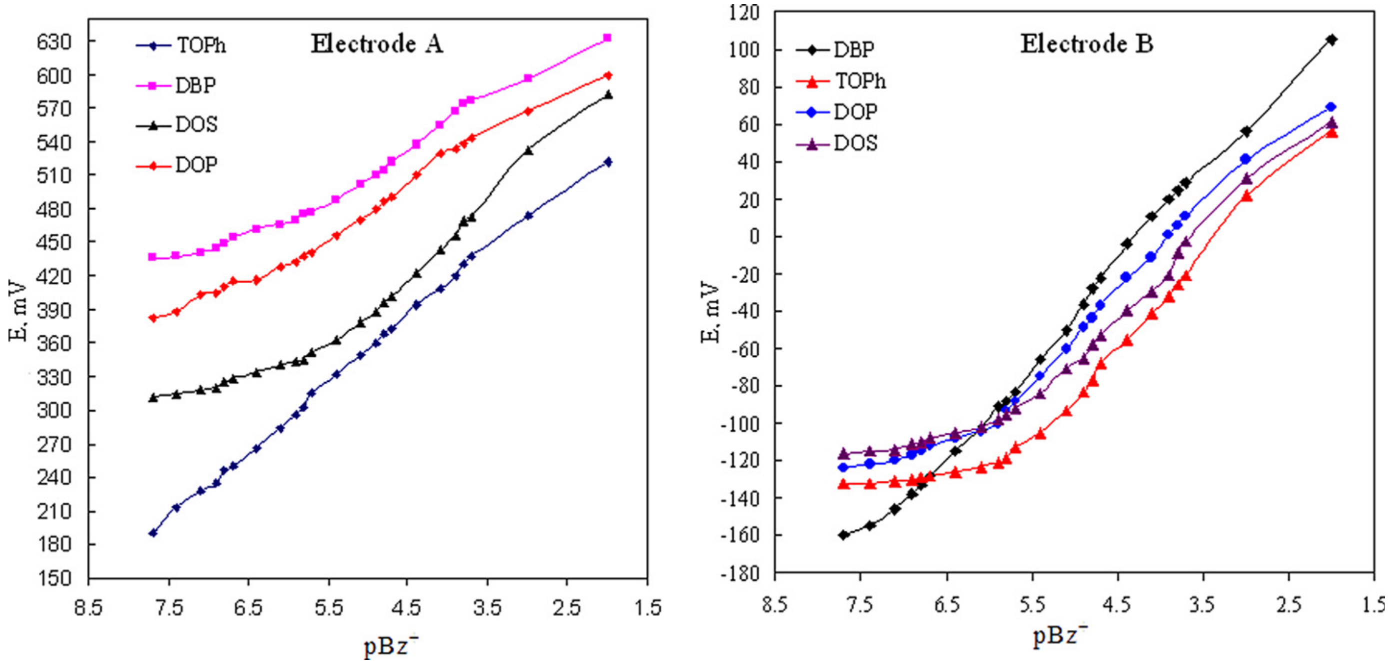


Fig. 2. Effect of different plasticizers on the response of electrode A and electrode B.

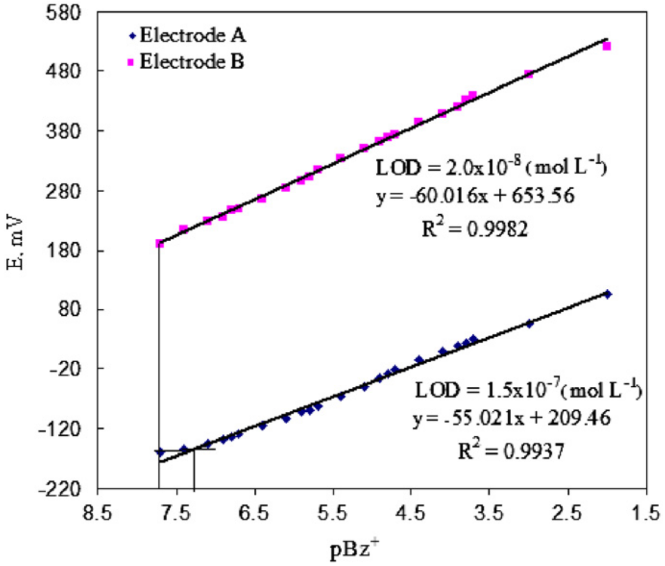


Fig. 3. Calibration graph, slope and limit of detection (LOD) of electrode A and electrode B.

50.8 wt% PVC, 48.1 wt% DBP and 0.1 wt% Na-TPB for electrode B exhibited the best response characteristics and the lowest detection limit. Therefore, these compositions were used to study various operation parameters of the electrodes. The electrochemical performance characteristics of these electrodes were systematically evaluated according to the International Union of Pure and Applied Chemistry (IUPAC) recommendations [31].

The potentiometric responses of the electrodes A and B were examined in the concentration range from 2.0×10^{-8} to 1.0×10^{-2} mol L^{-1} BzCl solutions. The calibration plots for these electrodes, represented in Fig. 3, show linearity over the concentration range from 2.0×10^{-8} to 1.0×10^{-2} mol L^{-1} and 2.0×10^{-7} to 1.0×10^{-2} mol L^{-1} and the limits of detection were 2.0×10^{-8} and 1.5×10^{-7} mol L^{-1} for electrodes A and B respectively. Comparison of the slopes, linear ranges and detection limits of the electrodes is given in Table 1. The results revealed that characteristics of solid contact electrode surpass the PVC electrode due to elimination of the internal solution.

3.2. *Effect of electrode bed*

To investigate the effect of the bed nature on the efficiency of coated wire electrodes, the optimized coating mixture was used for preparation of electrodes with different conductive beds, namely silver, copper, graphite and aluminum. After conditioning, each electrode was examined in the concentration range from 1.0×10^{-8} to 1.0×10^{-2} mol L^{-1} Bz^{+} solution. The dynamic range of concentration and the limit of detection of the electrodes were evaluated according to the IUPAC recommendations [31]. Examining the results compiled in Table 1, one can notice that all wires give inferior response towards BzCl as compared to that of silver wire. Ag wire-coated electrode has a slope 60 ± 0.3 mV/decade and a detection limit of 2.0×10^{-8} mol L^{-1}. This is attributed to low resistivity (1.62 μΩ cm^{-1}) of silver [17]. Therefore, silver wire was used as the inner solid contact for the electrodes in this study.

3.3. *Effect of diverse ions*

The selectivity coefficient is a summary of information concerning interferences on the electrode response in analytical applications. The response for the analyte must be as high as possible as compared to the response for foreign substances which must be very small so that the electrode exhibits Nernstian dependence on the primary ion over a wide concentration range. The selectivity of the ion-exchanger of the electrode depends on the selectivity of the ion-exchange process at the sensor-test solution interface and the mobilities of the respective ions in the matrix of the sensor.

Several methods such as fixed interference method, the separate solution method and the matched potential method (MPM) are used to determine the selectivity coefficients. International Union of Pure and Applied chemistry (IUPAC) recommended the separate solution method (SSM). However, it has been shown that

Table 2
Selectivity coefficients of various interfering ions for electrodes A and B.

	Electrode A		Electrode B	
Interfering ions	SSM	MPM	SSM	MPM
NH^{+}	2.53×10^{-4}	8.11×10^{-5}	5.15×10^{-4}	1.12×10^{-4}
Na^{+}	4.52×10^{-4}	3.63×10^{-4}	2.53×10^{-4}	2.15×10^{-4}
K^{+}	733 × 10-4	8.21×10^{-4}	4.12×10^{-4}	3.02×10^{-4}
Ag^{+}	5.11×10^{-4}	6.88×10^{-4}	3.33×10^{-4}	1.16×10^{-4}
Li^{+}	5.11×10^{-4}	5.23×10^{-4}	5.54×10^{-4}	1.96×10^{-4}
Pb^{+2}	5.25×10^{-4}	8.96×10^{-5}	4.11×10^{-4}	5.15×10^{-5}
Mg^{2+}	2.11×10^{-4}	4.11×10^{-5}	5.52×10^{-4}	3.19×10^{-5}
Ca^{2+}	7.48×10^{-4}	5.33×10^{-5}	6.28×10^{-4}	5.43×10^{-5}
Ba^{2+}	3.66×10^{-4}	7.30×10^{-5}	4.48×10^{-5}	1.15×10^{-6}
Zn^{2+}	2.25×10^{-4}	1.55×10^{-5}	3.56×10^{-5}	1.44×10^{-4}
Ni^{2+}	8.56×10^{-4}	4.51×10^{-5}	8.96×10^{-5}	2.55×10^{-5}
Cd^{2+}	4.25×10^{-4}	1.08×10^{-5}	6.48×10^{-5}	4.33×10^{-6}
Co^{2+}	8.95×10^{-4}	2.44×10^{-5}	2.52×10^{-4}	1.18×10^{-4}
Cu^{2+}	3.56×10^{-4}	2.88×10^{-5}	7.22×10^{-4}	5.22×10^{-4}
Pb^{2+}	3.22×10^{-4}	5.25×10^{-5}	1.05×10^{-4}	8.19×10^{-5}
Al^{3+}	3.66×10^{-4}	6.44×10^{-5}	2.13×10^{-4}	1.12×10^{-4}
Cr^{3+}	6.23×10^{-4}	5.72×10^{-5}	1.72×10^{-4}	1.10×10^{-4}
Hg^{+2}	5.68×10^{-4}	2.66×10^{-5}	1.46×10^{-4}	1.87×10^{-4}
CTAB	8.53×10^{-2}	8.84×10^{-2}	2.56×10^{-2}	4.05×10^{-2}
Praepagen HY	7.50×10^{-2}	6.77×10^{-2}	1.25×10^{-2}	2.33×10^{-2}
Sodium dodocyl Sulfate	1.44×10^{-5}	5.83×10^{-6}	2.59×10^{-5}	1.33×10^{-5}
Na-EDTA	3.82×10^{-6}	1.22×10^{-6}	5.47×10^{-6}	1.59×10^{-6}
TEA	–	3.78×10^{-6}	–	2.56×10^{-6}
Glycerin	–	1.41×10^{-7}	–	1.52×10^{-5}
Propylene glycol	–	5.50×10^{-7}	–	4.21×10^{-6}
Dexmethasone	–	6.12×10^{-7}	–	5.70×10^{-6}

this method suffers some limitations in terms of the values for ions of unequal charges, a non-Nernstain behavior of interfering ions [32]. Therefore another method named the "matched potential method (MPM)" was recommended especially when the primary ion and/or the interfering ion dissatisfy the Nernst response or when the involved ions are unequal in charge [33]. The values of the selectivity coefficients are listed in Table 2. They reflect a very high selectivity of each of these electrodes for benzalkonium cations over most of the tested species. We have recently found that the cationic surfactants cetyltrimethyl ammonium bromide (CTAB) and praepagen HY have strong effect on the slope and the working range in carbon paste electrode [12]. However, it was observed that this problem disappeared in the present electrodes. Drug formulations may contain flavoring agents, diluents and excipients, such as maltose, glucose and lactose. The results listed in Table 2 reveal that there were no significant interferences from any of the tested substances. Overall, the designed electrodes are useful for the intended measurements. The mechanism of selectivity is based mainly on the stereospecificity and electrostatic environment. It is dependent on the extent of fitting between the sites of the lipophilicity of the two competing species in the bathing solution side and the receptor of the ion-exchanger [34].

3.4. The effect of pH on the response of the electrodes

The influence of the pH of the solution on the response of the proposed electrodes was studied for 1.0×10^{-4} and 1.0×10^{-5} mol L^{-1} Bz^{+} ion in the pH range of 2.0–11.0. The pH was adjusted with 0.1 mol L^{-1} solutions of hydrochloric acid or sodium hydroxide. It can be seen from Fig. 4 that the variation in potential is acceptable in the pH range 4.8–8.0 for sensor A and from 2.8 to 8.3 for sensor B.

Nevertheless, sensor A at pH <4.8 and sensor B at pH <2.8 showed a nonlinear response with slight increase in the potential. This is likely due to the effect of the increase in the hydronium ion concentration on the electrode behavior. At high pH the OH^{-} ions penetrate the membrane and react with PM^{-} ions which are anions of the polyprotic acid (that contain a proton or more). Thus the equilibrium is disrupted and shifted to the right with the effect of gradual decrease of the ion-exchanger and a decrease in the concentration of the active ingredient of the sensor. This explanation is similar to that proposed recently [12].

3.5. Dynamic response time, reversibility, repeatability and life time of the electrodes

The dynamic response time is a significant parameter for an ion-selective electrode. The dynamic response time of the presented electrodes was measured according to IUPAC recommendation [31]. The response time may be defined as the time between addition of the analyte to the sample solution and the time when a limiting potential has been reached [31]. In this work, the response time of each electrode was measured by varying the Bz^{+} concentration over the range from 5.0×10^{-7} to 5.0×10^{-3} mol L^{-1}. As shown in Fig. 5, the electrodes reach equilibrium in about 5 s. At lower concentrations, the response time was longer and reached to 8 s and no change was observed up to 5 min.

On the other hand, in order to evaluate the reversibility of the proposed electrodes, the electrodes potentials of 1.0×10^{-5} mol L^{-1} and 1.0×10^{-4} mol L^{-1} Bz^{+} solutions were measured alternately in the same solution after making the proper treatment. The results, indicate that the potentiometric responses of the electrodes are reversible.

The repeatability of the potential reading for each electrode was examined by subsequent measurement in 1.0×10^{-5} mol L^{-1} Bz^{+} solution immediately after measuring the first set of solutions in 1.0×10^{-4} mol L^{-1} BzCl. The electrode potential for four replicate measurements in 1.0×10^{-5} mol L^{-1} solution of electrode A and B are 250 and -42 mV with a standard deviation of 1.47 and 1.54 respectively. The corresponding values in 1.0×10^{-4} mol L^{-1} solution were 305 and 8 mV with standard

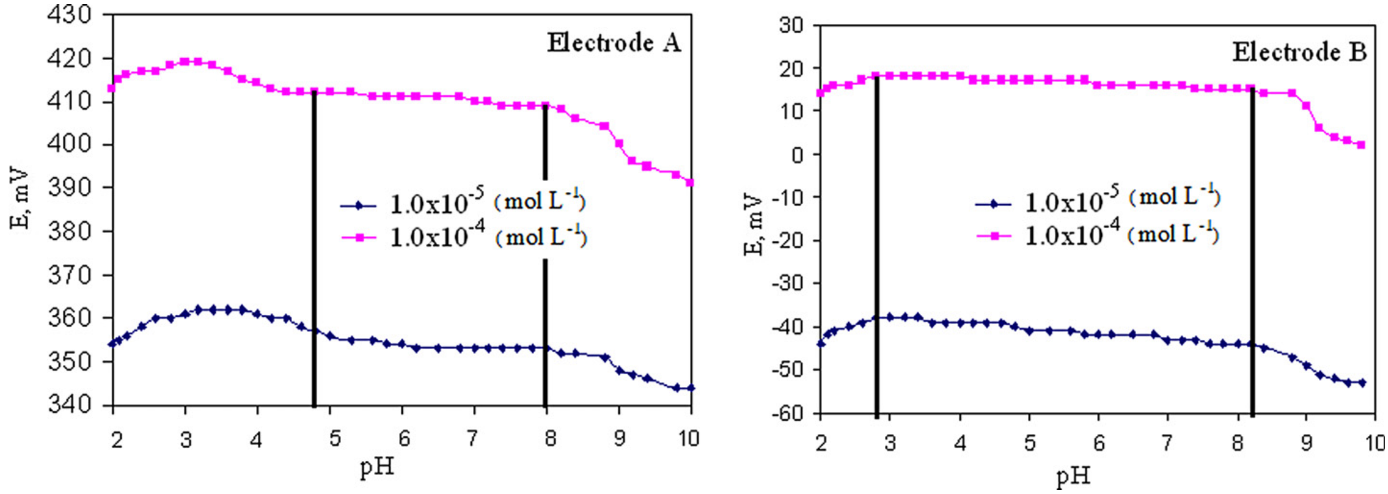


Fig. 4. Effect of pH of the test solution on the potential response of electrode A and electrode B.

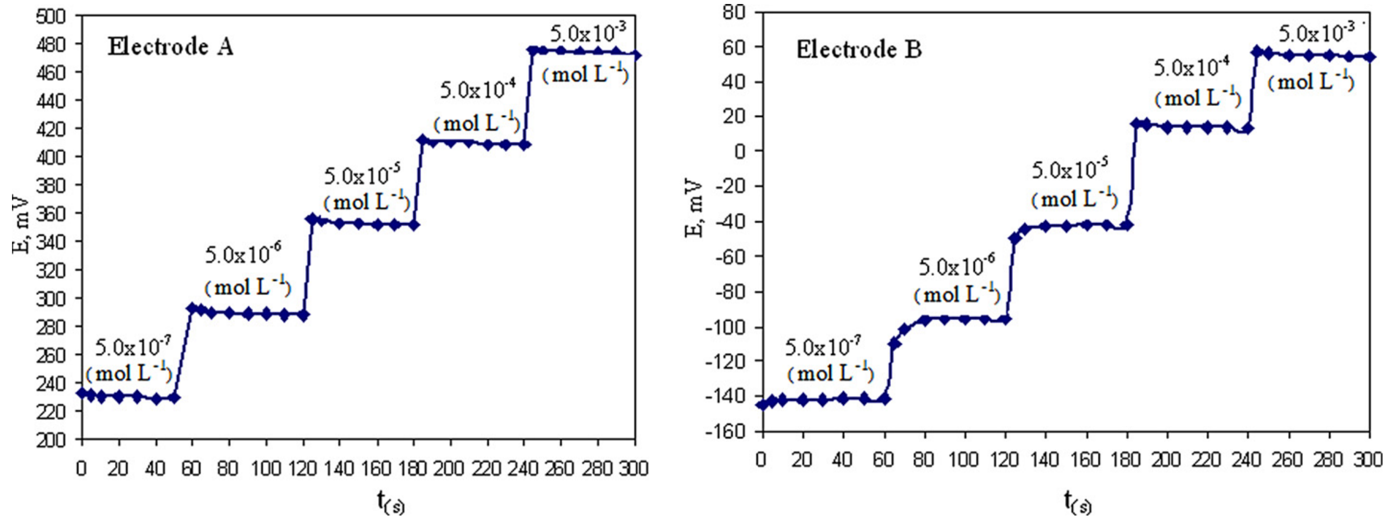


Fig. 5. Typical potential–time plot for response of electrode A and electrode B.

deviation of 0.59 and 0.85. This indicates excellent repeatability of the potential response of the electrodes.

The performance characteristics of the investigated electrodes were studied as a function of soaking time. The effect of soaking on the performance of the electrodes was studied by soaking each electrode in 10^{-3} mol L^{-1} solution of BzCl for variable intervals starting from 30 min reaching to 30 days. The slopes of the electrodes were observed to show gradual decrease after 5 days for electrode A (from 60 ± 0.3 to 54 ± 0.5 mV/decade) and 20 days for electrode B (decreased from 55 ± 1.2 to 50 ± 0.4 mV/decade). The life spans of the CWEs, in general, are less than those of the corresponding liquid contact electrodes. This may be attributed to poor mechanical adhesion of the PVC-based sensitive layer to the conductive bed [35].

3.6. *Effect of temperature*

To study the thermal stability of the electrodes, calibration graphs were constructed at different test solution temperatures of the test solution covering the range 20–55 °C. The slope, response time, concentration range and the detection limit were obtained from the calibration plot corresponding to each temperature. The results indicate that no appreciable change in the calibration characteristics of the electrodes was observed in the temperature range 20–55 °C.

3.7. *Analytical applications*

The designed sensors were utilized to determine BzCl in pharmaceutical preparations using the standard additions, calibration curve and potentiometric titration methods.

3.7.1. *Titration of benzalkonium chloride solution with Na-TPB solution*

The present electrodes were successfully applied as an indicator in potentiometric titration of 10.0 mL of 0.001 mol L^{-1} (3.58 mg) BzCl with 0.001 mol L^{-1} Na-TPB. The method for benzalkonium ion (Bz^+) titration is based on the quantitative combination of Bz^+ with TPB^- and the decrease of Bz^+ concentration by precipitation with Na-TPB standard solution. The resulting titration curve is shown in Fig. 6. It is clear that the amount of Bz^+ ion can be an accurately determined with these electrodes.

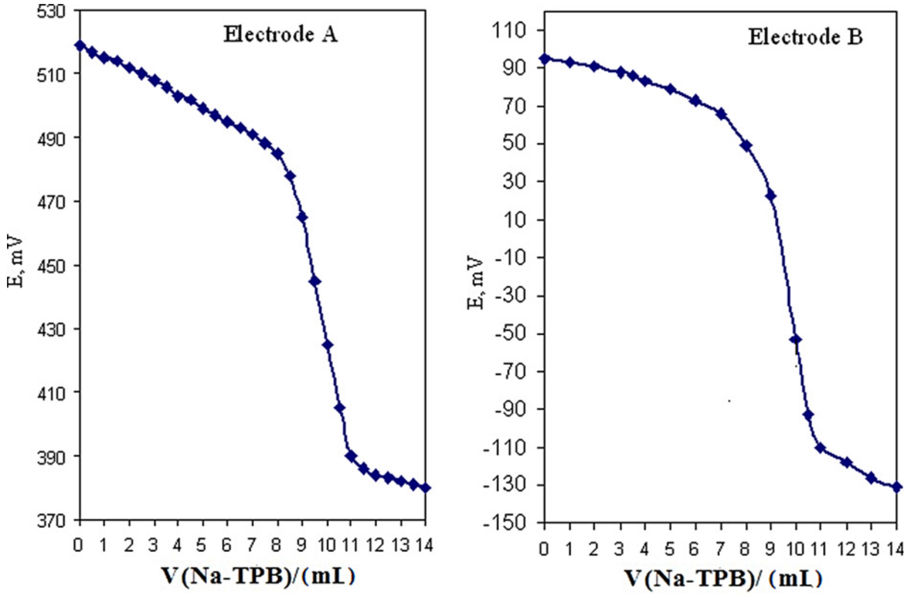


Fig. 6. Potentiometric titration of 3.58 mg BzCl with Na-TPB as titrants using electrode A and electrode B.

Table 3
Analysis of BzCl in various samples using standard addition and calibration curve methods.

	Taken (mol L^{-1})	Found (mol L^{-1})	*X* %	R.SD.%
Electrode A				
Fml (Eye drop)	s(1.0×10^{-5})	(9.75×10^{-6})	97.5	1.23
	c(1.3×10^{-4})	(1.27×10^{-4})	97.7	0.98
Oflox (Eye drop)	s(1.0×10^{-5})	(1.02×10^{-5})	102.0	1.56
	c(1.0×10^{-5})	(9.95×10^{-5})	99.5	1.14
Dextrol (Ear drop)	s(1.0×10^{-5})	(9.77×10^{-4})	97.7	0.56
	c(1.1×10^{-4})	(1.08×10^{-4})	98.1	0.87
Lyse (Nasal drop)	s(1.0×10^{-5})	(1.00×10^{-5})	100.0	1.02
	c(1.0×10^{-5})	(9.85×10^{-6})	98.5	0.98
Otrivin baby (Nasal drop)	s(1.0×10^{-5})	(9.95×10^{-6})	99.5	0.77
	c(1.0×10^{-5})	(1.01×10^{-4})	101.0	1.05
Isopto_Maxidex (Eye drop)	s(1.0×10^{-5})	(9.90×10^{-6})	99.0	1.28
	c(1.0×10^{-5})	(1.00×10^{-5})	100.0	0.63
DAC (liquid detergent)	s(1.0×10^{-5})	(9.78×10^{-6})	97.8	0.84
	c(1.0×10^{-5})	(9.87×10^{-6})	98.7	0.79
Electrode B				
Fml (Eye drop)	s(1.0×10^{-5})	(9.88×10^{-6})	98.8	1.39
	c(1.1×10^{-4})	(1.07×10^{-4})	97.3	0.98
Oflox (Eye drop)	s(1.0×10^{-5})	(1.01×10^{-5})	101.0	0.65
	c(1.0×10^{-5})	(1.0×10^{-5})	100.0	0.96
Dextrol (Ear drop)	s(1.0×10^{-5})	(9.85×10^{-6})	98.5	1.25
	c(1.1×10^{-4})	(1.07×10^{-4})	97.3	0.91
Lyse (Nasal drop)	s(1.0×10^{-5})	(1.00×10^{-5})	100.0	0.78
	c(1.0×10^{-5})	(9.78×10^{-6})	97.8	0.51
Otrivin baby (Nasal drop)	s(1.0×10^{-5})	(9.98×10^{-6})	99.8	0.95
	c(1.0×10^{-5})	(9.95×10^{-6})	99.5	0.88
Isopto_Maxidex (Eye drop)	s(1.0×10^{-5})	(9.88×10^{-6})	98.8	1.33
	c(1.0×10^{-5})	(1.00×10^{-5})	100.0	1.02
DAC (liquid detergent)	s(1.0×10^{-5})	(9.93×10^{-6})	99.3	0.98
	c(1.0×10^{-5})	(1.01×10^{-4})	101.0	0.75

S: standard addition method, C: calibration curve, The number of replicate measurements=5, X: recovery, R.S.D.: relative standard deviation.

3.7.2. *Determination of benzalkonium chloride in pharmaceutical formulations*

The proposed electrodes were used in the standard addition and the calibration methods for determination of BzCl content in pure solutions and in its pharmaceutical formulations (eye, nasal and ear drops). As can be seen in Table 3, the recovery of BzCl is almost quantitative.

4. Conclusions

Two kinds of potentiometric (PVC and a silver-coated wire) electrodes were constructed for determination of BzCl and a comparison was made between them. The sensors show favorable performance characteristics with short response times (~5 s), low detection limits of 1.0×10^{-5} mol L^{-1} and 1.0×10^{-6} mol L^{-1} over the concentration range from 1.0×10^{-5} to 1.0×10^{-2} mol L^{-1} and 1.0×10^{-6}–1.0×10^{-3} mol L^{-1}, for PVC membrane and coated wire electrodes respectively. Clearly, the coated wire electrode shows a lower detection limit due to its diminished current flux. The sensors were effectively used for determination of BzCl in pharmaceutical preparations (eye, ear and nasal drops).

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