

Potentiometric determination of Benzydamine hydrochloride using PVC membrane and coated wire sensors in pure form, pharmaceutical compounds and biological fluids.

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Abstract- The construction and electrochemical response characteristics of PVC membrane and coated wire sensors for the determination of Benzydamine hydrochloride (Benz) are described. PVC membrane sensors, include sensors 1, 2 and 3, and coated-wire sensors include sensors 4, 5 and 6. Sensors 1 and 4 based on benzydamine - phosphotungstate (Benz-PTA) as ion-pair, sensors 2 and 5 based on benzydamine - phosphomolybdate (Benz-PMA) as ion-pair and sensor 3 and 6 based on benzydamine - reineckate (Benz-RN) as ion-pair. Sensors 1, 2 and 3 (PVC membrane sensors) have a linear concentration range from 7.0×10^{-6} to 1.0×10^{-2} , 1.0×10^{-5} to 1.0×10^{-2} and 1.0×10^{-5} to 1.0×10^{-2} mol L⁻¹, with a Nernstian slope of 58.6 ± 0.3 , 59 ± 0.4 and 58.7 ± 0.2 mV/decade and a detection limit of 5.0×10^{-6} , 7.2×10^{-6} and 1.0×10^{-5} mol L⁻¹, respectively. Sensors 4, 5 and 6 (coated-wire sensors) have the same linear concentration range from 1.0×10^{-6} to 1.0×10^{-2} mol L⁻¹, with the same detection limit of 1.0×10^{-6} mol L⁻¹ and with a Nernstian slope of 58.9 ± 0.1 , 60.0 ± 0.5 and 59.5 ± 0.4 mV/decade, respectively. The response is independent of the pH of test solution within the range 3–8 for PVC membrane sensors and within 2-8 for coated-wire(CW) sensors. All sensors show fast response time which is 5, 3, 3, 8, 6 and 7 s for sensors 1, 2, 3, 4, 5 and 6, respectively. The sensors showed good selectivity towards benzydamine with respect to large numbers of species. . The sensors have been applied to the determination of benzydamine in pure solution, pharmaceutical compounds and biological fluids.

keywords: Benzydamine hydrochloride; Potentiometry; Sensors; Biological fluids.

1 Introduction

Benzydamine (1-benzyl-3-(3-dimethylamino-propoxy)-1H-indazole hydrochloride) is a tertiary amine (Fig. 1). Benzydamine (Benz) is a non-steroidal drug that reportedly possesses analgesic, anesthetic, anti-inflammatory, and antimicrobial properties [1]. Several analytical techniques have been used to determine benzydamine hydrochloride in pharmaceutical products including non-aqueous titration method [2,3], spectrophotometric methods [4-6], high performance liquid chromatography [7-11], and amperometric biosensor [12]. 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 also 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.

The most common type of ISEs employed for drug analysis is the conventional liquid membrane electrode. The construction of a liquid 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 [13]. The way to reduce the size of the conventional ISEs and to overcome the abovementioned limitations is the use of coated-wire (CW) sensors. Coated-wire sensors were first introduced by Cattrall and Freiser in 1971 [14]. A suitable polymeric membrane, containing a dissolved electro-active material was directly coated on a conducting substrate (generally a metal, although any material, whose conductivity is substantially higher than that of the film can be used) [15]. These sensors have certain advantages over conventional ones such as the small size, simple construction, lower cost, and ability to work in any position. Furthermore, this type of sensors allows for low detection limit, which was attributed to the absence of trans-membrane ion fluxes [16, 17]. No studies in the literature have reported potentiometric sensors for determination of benzydamine hydrochloride yet.

The present study is concerned with preparation, characterization and application of simple potentiometric sensors for rapid determination of Benz in pure and dosage forms. Both PVC and Coated-wire sensors were fabricated and subjected to a series of tests to select sensors possessing the most favorable analytical characteristics. The developed sensors were applied in the potentiometric determination of Benz in batch analysis using standard addition and potentiometric titration.

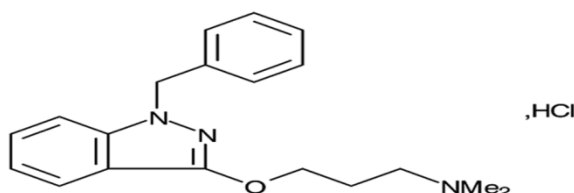


Fig. 1 The chemical structure of benzydamine hydrochloride.

2 Experimental

2.1 Reagents and materials

All chemicals were of analytical grade. Double distilled water was used throughout all experiments. Pure grade Benz and the pharmaceutical preparation TANTUM VERDE were provided by Egyptian International Pharmaceutical Industry Co. (EIPICO). Phosphotungstic acid (PTA), ammonium reineckate (RN), poly(vinyl chloride) of high molecular weight (PVC), dioctyl sebacate (DOS), dioctyl adipate (DOA), sodium tetraphenylborate (NaTPB), and tricresyl phosphate (TCP) were obtained from Fluka (U.S.A.). Phosphomolybdic acid (PMA), tetrahydrofuran (THF), dibutyl phthalate (DBP), and dioctyl phthalate (DOP) were purchased from Merck (Germany). The metal salts were provided by BDH as nitrates or chlorides. Stock solutions of the metal salts were prepared in bidistilled water and standardized when-ever necessary. In the analysis of biological fluids, human urine and plasma were used, plasma was obtained from Regional Blood Transfusion Services, Beni-Suef, Egypt and used within 24h.

2.2 Apparatus

Laboratory potential measurements were performed using Metrohm titroprocessor model 702. Metrohm PH electrode (6.0232.100). Silver-silver chloride double - junction reference electrode (Metrohm 6.0222.100) in conjugation with different drug ion selective electrode was used. A mLW W20 circulator thermostat was used to control the temperature of the test solutions.

2.3 Preparation of the ion-pairs

The ion pairs, Benz-PTA, Benz-PMA and Benz -RN were prepared by mixing 100 mL 10^{-2} mol L $^{-1}$ Benz solution with 100 ml of 10^{-2} mol L $^{-1}$ of phosphotungstic acid, Phosphomolybdic acid or ammonium reineckate. The formed precipitates were filtered, washed thoroughly with bidistilled water and dried at room temperature.

2.4 Preparation of PVC membrane sensors

The sensor were prepared by dissolving varying amounts of the ion- pair and PVC in 5 mL THF. To these, solvent mediators, viz. DBP, DOS, TCP ,DOA and DOP were added to get membranes of different compositions. The mixture was stirred with a magnetic stirrer. When the solution became viscous it was poured into a 6.0 cm Petri dish. The solution was then allowed to evaporate for 24 h at room temperature. Transparent membranes of about 0.2 mm thickness were obtained. 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 sensor body was filled with a solution of 1×10^{-1} mol L⁻¹ NaCl and 1×10^{-2} mol L⁻¹ Benz. The sensor was preconditioned before use by soaking in bidistilled for 24 h. The ratio of membrane ingredients, time of contact and concentration of conditioning solution were optimized so that the potentials recorded were reproducible and stable.

2.5 Preparation of the coated-wire membrane sensors

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 sensor was preconditioned by soaking for 30 min in 10^{-3} mol L⁻¹ Benz solution.

2.6 Sensors calibration

The calibration of the sensors under investigation was established by immersing the working sensors in conjunction with Ag/AgCl reference sensor in 50 ml beakers containing known aliquots of 1×10^{-7} - 1×10^{-2} mol L⁻¹ Benz standard solution. The potential reading was plotted against the negative logarithmic value of Benz concentrations. The established calibration graph was used for subsequent determination of unknown Benz concentrations.

2.7 Effect of pH

The effect of pH on the response of the investigated sensors was studied using 10^{-3} and 10^{-4} mol L⁻¹ Benz solutions over the pH range of 1–12. This is done by immersing the sensors and pH was gradually increased or decreased by addition of very small volumes of diluted NaOH or HCl solutions, respectively. The potential obtained at each pH was recorded.

2.8 Effect of temperature

The effect of temperature on the performance of the potentiometric sensors was evaluated by construction of calibration curves at different temperatures (20-60°C).

2.9 Conductometric Measurements

Conductometric titrations were followed with a Jenway conductivity meter. 50 mL of 1×10^{-3} mol L⁻¹ Benz solution was transferred to the 100 mL cell and the solution titrated against a 1×10^{-2} mol L⁻¹ PTA, PMA or RN solution using a microburette. The conductance of the solution was measured after thorough stirring after each addition (2 min, intervals). Conductance values were corrected by multiplying by the dilution coefficient and plotted versus molar ratio. The titration plot showed a break which corresponds to the stoichiometry of the ion-pair.

2.10 Determination of Benz in pure form and pharmaceutical formulation

The proposed sensors were found to be useful in the potentiometric determination of Benz in pure solution and in pharmaceutical preparation by using the standard addition and potentiometric titration methods.

In the standard addition method, known increments of Benz standard solution were added to constant volume of samples of different concentrations. The voltage was first measured in the pure sample, then the standard was added and the solutions were mixed well; a second reading was taken. From the change in potential readings for each increment the concentration of the unknown sample was calculated using the following equation [18].

$$C_x = \{C_s[V_s]/(V_x - V_s)\} \times \{10n(\Delta E/s) - [(V_x)/(V_s - V_x)]\}^{-1} \quad (1)$$

Where C_x and V_x are the concentration and the volume of unknown, respectively. C_s and V_s are the concentration and the 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.

In the potentiometric titration aliquots of the drug solution containing different weights from drug mg transferred to a 100-mL beaker. A standard solution of PTA, PMA and RN were used as a titrant and the titration is monitored using proposed sensors as indicator electrodes conjugated with Ag/AgCl as the reference electrode. The potential values were plotted against the volume of the titrant added and the end points were determined from the S-shaped curves using the first derivative plots.

2.11 Determination of Benz in spiked urine and plasma samples

Different amounts of Benz and 5 mL urine or plasma 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 Benz by the standard addition method.

3 Results and discussion

3.1 Effect of membrane composition

The composition of the ion-pairs were found to be 1 : 1 in case of Benz-RN and 3:1 in case of both Benz-PTA and Benz-PMA as indicated by conductometric titrations (Fig. 2).

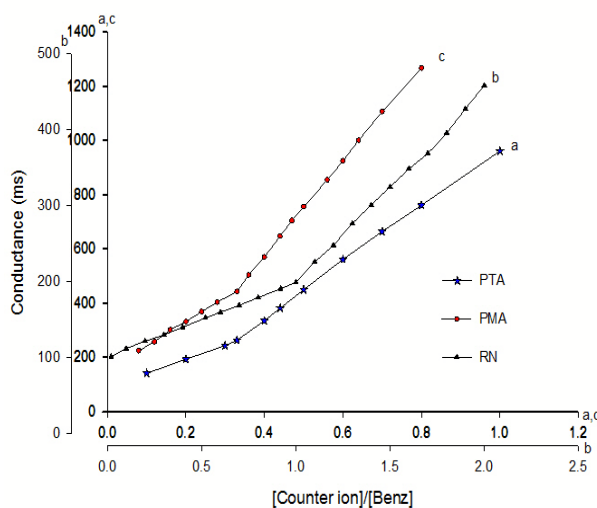


Fig. 2 Conductometric titration curve of 1×10^{-2} mol L⁻¹ Benz against 1×10^{-2} mol L⁻¹ PTA, RN and PMA.

The response characteristics of ion-selective sensors depend significantly on the nature of ion-pairs and their lipophilicities, the type of plasticizers and the amount of additives used. To evaluate the incidence of membrane parameters on sensor responses we explored the influence of the ion-pairing agent nature (PTA, PMA and RN), nature of plasticizers by testing five different agents (DBP, DOP, DOS, DOA and TCP) and amount of additives, such as sodium tetraphenylborate. Several membranes of a varying nature and ratio of ion-exchanger/PVC/plasticizer/NaTPB were prepared and their response characteristics were evaluated according to the IUPAC recommendations [19, 20]. The results were listed in Table 1.

Table 1 Effect of the content of ion pairing agents on the performance of the proposed sensors.

Sensor no.	Composition (%)				Sensor Characteristics				
	Ion-Pair	PVC	DBP	NaTPB	Slope (mV/decade)	L.R (mol L ⁻¹)	LOD (mol L ⁻¹)	RSD (%)	r ²
PVC sensors									
Benz-PTA									
1.	3.0	48.5	48.5	-	52.8	1.0 x10 ⁻⁵ -1.0x10 ⁻²	1.0 x10 ⁻⁵	0.45	0.996
2.	5.0	47.5	47.5	-	56.8	1.0 x10 ⁻⁵ -1.0x10 ⁻²	7.0 x10 ⁻⁶	0.66	0.998
3.	7.0	46.5	46.5	-	56.8	8.0 x10 ⁻⁶ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.35	0.997
4.	9.0	45.5	45.5	-	57.5	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.0 x10 ⁻⁶	1.56	0.998
5.	12.0	44.0	44.0	-	58.6	7.0 x10⁻⁶-1.0x10⁻²	5.0 x10⁻⁶	0.51	0.999
6.	15.0	42.5	42.5	-	57.3	7.0 x10 ⁻⁶ -1.0x10 ⁻²	5.0 x10 ⁻⁶	1.01	0.999
Benz-PMA									
7.	3.0	48.5	48.5	-	50.9	1.0 x10 ⁻⁵ -1.0x10 ⁻²	1.0 x10 ⁻⁵	0.79	0.999
8.	5.0	47.5	47.5	-	59.0	1.0 x10⁻⁵-1.0x10⁻²	7.2 x10⁻⁶	0.74	0.999
9.	7.0	46.5	46.5	-	53.3	8.0 x10 ⁻⁶ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.82	0.999
10.	9.0	45.5	45.5	-	52.6	8.0 x10 ⁻⁶ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.52	0.999
Benz-RN									
11.	0.3	49.9	49.9	-	47.6	1.0 x10 ⁻⁵ -1.0x10 ⁻²	1.0 x10 ⁻⁵	1.42	0.998
12.	0.5	49.8	49.8	-	52.4	1.0 x10 ⁻⁵ -1.0x10 ⁻²	7.2 x10 ⁻⁶	0.98	0.998
13.	1.0	49.5	49.5	-	49.9	1.0 x10 ⁻⁴ -1.0x10 ⁻²	5.0 x10 ⁻⁵	1.6	0.997
14.	0.5	49.7	49.7	0.2	53.6	1.0 x10 ⁻⁵ -1.0x10 ⁻²	7.0 x10 ⁻⁶	1.2	0.998
15.	0.5	49.6	49.6	0.3	58.7	1. x10⁻⁵-1.0x10⁻²	5.0 x10⁻⁶	0.30	0.999
16.	0.5	49.6	49.6	0.4	52.7	1.0 x10 ⁻⁵ -1.0x10 ⁻²	4.0 x10 ⁻⁵	0.57	0.998
Coated-wire sensors									
Benz-PTA									
Effect of sensor bed using (12%)Benz-PTA									
17.	Silver	-	-	-	58.9	1.0 x10⁻⁶-1.0x10⁻²	1.0 x10⁻⁶	0.10	0.999
18.	Platinum	-	-	-	52.6	1.0x10 ⁻⁵ -1.0x10 ⁻²	5.4 x10 ⁻⁶	1.62	0.996
19.	Graphite	-	-	-	51.9	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.78	0.990
20.	Copper	-	-	-	54.0	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.67	0.995
21.	Aluminum	-	-	-	49.2	1.0 x10 ⁻⁵ -1.0x10 ⁻²	6.3 x10 ⁻⁶	0.77	0.991
BENZ-PMA									
22.	5.0	47.5	47.5	-	60.0	1.0 x10⁻⁶-1.0x10⁻²	1.0 x10⁻⁶	0.84	0.997
BENZ-RN									
23.	0.5	49.6	49.6	0.3	59.5	1.0 x10⁻⁶-1.0x10⁻²	1.0 x10⁻⁶	0.68	0.998

3.2 Effect of the ion-pair

The ion-pair is the key constituent of the membrane and is responsible for the sensor response and performance. It should have rapid exchange kinetics and adequate complex formation constants in the membrane. Also, it should be well soluble in the membrane matrix and have a sufficient lipophilicity to prevent leaching from the membrane into the sample solution [21]. Several membranes based on different ion pairs and different compositions were tested. The slopes, concentration range and detection limits are listed in Table 1 and the calibration curves are shown in Fig. (3). The results clearly indicate that by increasing the ion pair percentage the slope and the sensitivity of the sensor increases until the value of 12%, 5%, and 0.5% for Benz-PTA, Benz-PMA and Benz-RN, respectively. However, further increase of the ion-exchangers over this percentage resulted in a diminished response slope

of the sensor, most probably due to some inhomogeneities and possible saturation of the membrane [22]. The electrochemical Performance characteristics of the proposed sensors were listed in table 2.

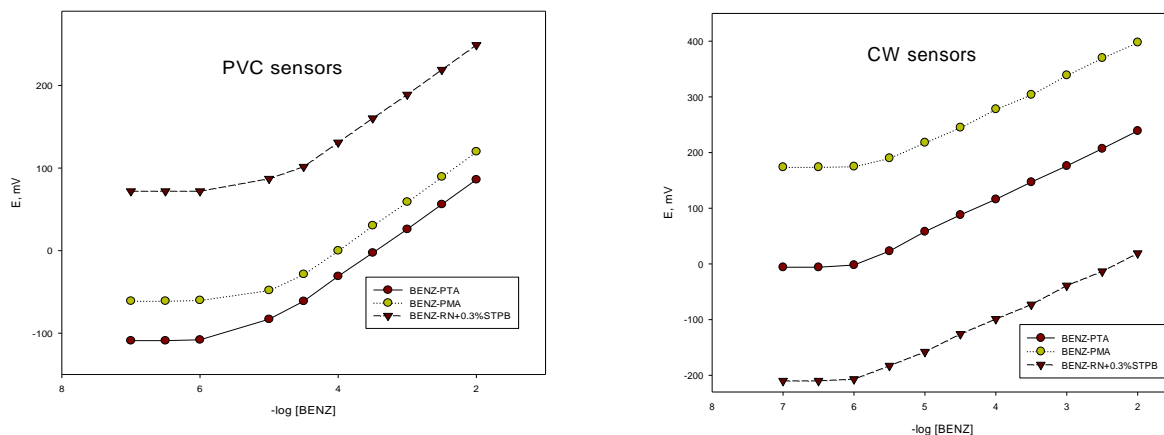


Fig. 3 Calibration graphs for PVC and CW sensors at optimum membrane composition.

3.3 Effect of additive

Additives such as lipophilic anions improve the potentiometric behavior of certain selective sensors not only by reducing the ohmic resistance and improving the response behavior and selectivity, but also, in cases where the extraction capability of the ion-pair is poor, by enhancing the sensitivity of the membrane sensor. Furthermore, additives may catalyze the exchange kinetics at the sample-membrane interface [23]. It is clear that the sensitivity and slope increased from 52.43 mV/decade to 58.7 mV/decade by adding trace amount of sodium tetraphenylborate 0.3%. However, increasing the amount of additive shows no beneficial influence on the membrane sensor response.

3.4 Effect of sensor bed

The efficiency of coated-wire sensors depends significantly on the nature of sensor bed, the optimized coating mixture was used for preparation of sensors with different conductive beds, namely silver, copper, graphite, platinum and aluminum. The results indicated that the silver wire-coated sensor has higher slope and lower detection limit compared with other tested wires (Table 1). This is attributed to low resistivity ($1.62 \Omega \text{ cm}^{-1}$) of silver. Therefore, silver wire was used as the inner solid contact for the sensors in this study [24].

3.5 Effect of internal filling solution

The potential response of the PVC sensors for Benz cation based on Benz-RN ion-pair was studied at different concentrations of internal solution (1.0×10^{-2} to $1.0 \times 10^{-4} \text{ mol L}^{-1}$ Benz). It was found that the best results in terms of slope and working concentration range have been obtained with internal solution of concentration $1.0 \times 10^{-4} \text{ mol L}^{-1}$. Thus, $1.0 \times 10^{-4} \text{ mol L}^{-1}$ concentration of the reference solution was quite appropriate for the smooth functioning of the proposed sensors.

Table 2 Response characterization of the proposed sensors.

Parameters	PVC sensors			Coated-wire sensors		
	Sensor1 (PTA)	Sensor2 (PMA)	Sensor3 (RN+ 0.3%NaTPB)	Sensor4 (PTA)	Sensor5 (PMA)	Sensor6 (RN+ 0.3%NaTPB)
Slope (mV/decade)	58.6	59.0	58.70	58.9	60.0	59.5
Correlation coefficient (r^2)	0.999	0.999	0.999	0.999	0.997	0.998
Detection limit (mol L^{-1})	5.0×10^{-6}	1.0×10^{-6}	1.0×10^{-5}	1.0×10^{-6}	1.0×10^{-6}	1.0×10^{-6}
Response time (s)	5	3	3	8	6	7

Working pH range	3-8	3-8	3-8	2-8	2-8	2-8
Life time (days)	63	25	31	4	4	4
SD (%)	0.3	0.44	0.18	0.06	0.51	0.4
RSD (%)	0.51	0.74	0.3	0.1	0.84	0.68
Thermal coefficient(V/ ⁰ C)	0.00056	0.00054	0.00071	0.0005	0.00017	0.00019

3.6 Effect of plasticizer

The plasticizer to be used in membrane should exhibit high lipophilicity, have high molecular weight, low tendency for exudation from the polymer matrix, low vapor pressure and high capacity to dissolve the substrate and other additives present in the membrane. Furthermore, it is a well established fact that the properties of plasticizer have a great influence on the sensitivity, selectivity detection limit and linearity of ISEs. Several plasticizers including DBP, DOS, DOP, DOA and DBP were tested. The best performance was achieved using DBP as membrane plasticizer and the result are summarized in Table 3.

Table 3 Effect of the plasticizers on Benz responsive sensors.

Ion-pair	Composition % w/w		Slope	Linear range	LOD	RSD
	PVC	plasticizer	mV/ decade	(mol L ⁻¹)	(mol L ⁻¹)	(%)
Benz-PTA sensors						
12.0	44	DOA	54.7	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.32
12.0	44	DBP	58.6	7.0 x10 ⁻⁶ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.51
12.0	44	DOP	54.1	1.0 x10 ⁻⁵ -1.0x10 ⁻²	4.0 x10 ⁻⁶	0.70
12.0	44	DOS	50.2	1.0 x10 ⁻⁵ -1.0x10 ⁻²	4.0 x10 ⁻⁶	0.40
12.0	44	TCP	54.7	1.0 x10 ⁻⁶ -1.0x10 ⁻²	1.0 x10 ⁻⁶	0.77
Benz-PMA sensors						
5.0	47.5	DOA	51.4	1.0 x10 ⁻⁴ -1.0x10 ⁻²	3.16 x10 ⁻⁵	0.68
5.0	47.5	DBP	59.0	1.0 x10 ⁻⁶ -1.0x10 ⁻²	1.0 x10 ⁻⁶	0.74
5.0	47.5	DOP	52.6	8 x10 ⁻⁵ -1.0x10 ⁻²	3.2 x10 ⁻⁵	0.29
5.0	47.5	DOS	48.5	1.0 x10 ⁻⁵ -1.0x10 ⁻²	1.0 x10 ⁻⁵	0.92
5.0	47.5	TCP	52.9	1.0 x10 ⁻⁴ -1.0x10 ⁻²	3.9 x10 ⁻⁵	0.48
Benz-RN+0.3 % NaTPB sensors						
0.5	49.6	DOA	53.4	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.29
0.5	49.6	DBP	58.7	3.16 x10 ⁻⁶ -1.0x10 ⁻²	1.0 x10 ⁻⁵	0.30
0.5	49.6	DOP	51.6	1.0 x10 ⁻⁵ -1.0x10 ⁻²	4.0 x10 ⁻⁶	0.58
0.5	49.6	DOS	54.3	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.2 x10 ⁻⁶	0.61
0.5	49.6	TCP	50.0	1.0 x10 ⁻⁵ -1.0x10 ⁻²	5.0 x10 ⁻⁶	0.51

3.7 Effect of pH

Since pKa of Benz is 9.26 [25], therefore at pH 7.8 Benz is nearly completely ionized, i.e. Benz will be in the cationic form. The concentration distribution diagram for Benz species is constructed using SPECIES program [26] (Fig. 4). Effect of pH of the test solution on the potential response of the CW membrane sensors is shown in Fig. 5. The potential pH profile obtained indicates that the potential remains constant in the pH range 3-8 and 2-8 for PVC and CW sensors, respectively. At lower pH values the decrease in mV readings may be attributed to the interference from hydronium ion and may also be due to leaching of the ion exchangers in acidic media. On the other hand the decrease in mV at higher pH may be due to base precipitates in the test solution and consequently, the concentration of unprotonated species gradually increased .

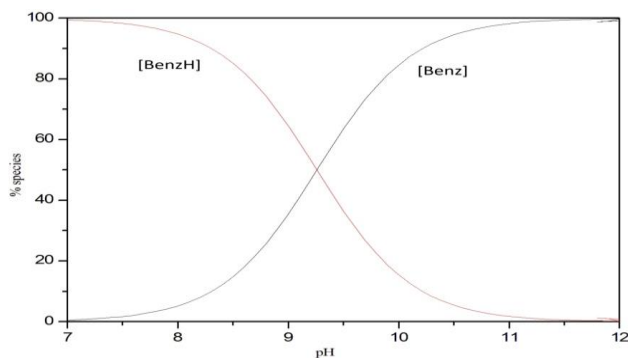


Fig. 4 Representative concentration distribution diagram for paroxetine hydrochloride species

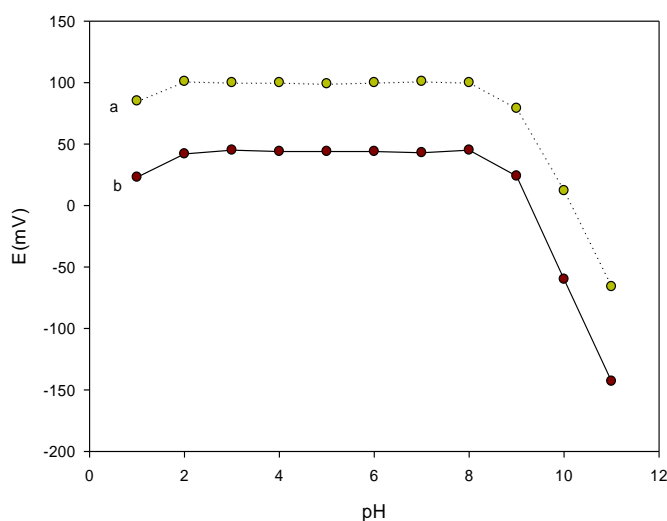


Fig. 5 Effect of pH on the performance of Benz-PMA CW sensor : (a) $1.0 \times 10^{-3} \text{ mol L}^{-1}$ Benz and (b) $1.0 \times 10^{-4} \text{ mol L}^{-1}$ Benz.

3.8 Dynamic response time, reversibility and memory effect

The dynamic response time of the presented sensors was measured according to IUPAC recommendation. The practical response time was recorded by changing solution with different Benz concentrations from 1.0×10^{-6} to $1.0 \times 10^{-2} \text{ mol L}^{-1}$. The actual potential versus time is shown in Fig. (6). The proposed sensors have very short response time of 3–5 s and 6–8 s for PVC and CW sensors, respectively. To evaluate the reversibility of the sensor, a similar procedure in the opposite direction was adopted. The measurements were performed in the sequence of high to low sample concentrations. The results indicate that the potentiometric responses of the sensors are reversible and had no memory effect.

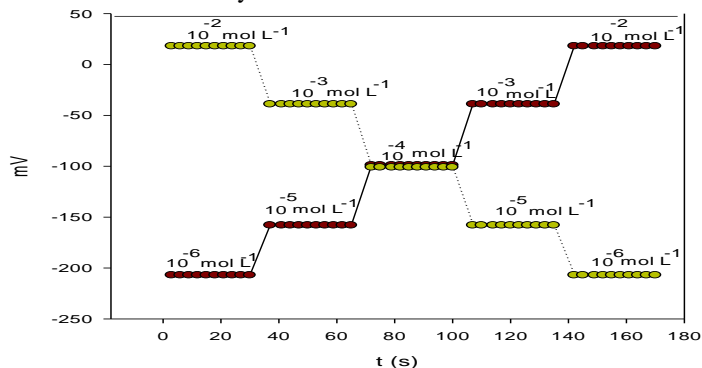


Fig. 6 Potential–time plot for the response of Benz-RN/0.3% NaTPB CW sensor.

3.9 Life time

The life time of the investigated sensors was studied by periodically constructing the calibration graphs under optimum conditions in the concentration range of 10^{-7} - 10^{-2} mol L⁻¹ of Benz on different days. For sensors under investigation it was found that PVC sensors (sensors no. 1, 2 and 3) have a life time of 63, 25 and 31 days, respectively and CW sensors have 4 days. After preparation of the proposed sensors, PVC sensors were kept at 4 °C in distilled water and directly used for potentiometric measurements. Results showed that obtained slopes decreased gradually if CW sensors were conserved in 1.0×10^{-3} mol L⁻¹ of Benz standard solution when not in use. For this reason, unused sensors were kept dry. It was established that continuous soaking had a negative impact on the response of the sensor due, probably, to the leaching of the active ingredients (ion-exchanger and plasticizer) to the bathing solution [27]. The life spans of the CW sensors, in general, are less than those of the corresponding liquid contact sensors. This may be attributed to poor mechanical adhesion of the PVC-based sensitive layer to the conductive bed [28].

3.10 Selectivity

Potentiometric selectivity coefficient refers to the ability of the ISE to differentiate a particular (primary) ion from others (interfering ions) [29]. The selectivity coefficients were determined by the modified separate solution method using the rearranged Nicolsky equation [30,31]:

$$\log K^{\text{pot}}_{\text{BENZ},\text{Jz}^+} = ((E_1-E_2)/S) + (1 + (z_1/z_2)) \log a$$

Where, E_1 is the potential measured in 1×10^{-3} mol L⁻¹ Benz, E_2 the potential measured in 1×10^{-3} mol L⁻¹ of the interfering ions, z_1 and z_2 are the charges of Benz and interfering species, respectively and S is slope of the sensor calibration plot. The selectivity sequence significantly differs from the so called Hofmeister selectivity sequence [32] (i.e. selectivity solely based on lipophilicity of cation). Also, the Matched Potential Method (MPM) is used for determination of selectivity coefficients in case of neutral species (sugars, urea and amino acids). As shown in Table 4 the results obtained of the proposed sensors display high selectivity for Benz cations and lower response of the interfering species present in solutions. The results also indicate that there was no serious interference from sugars, urea and amino acids due to the differences in polarity and lipophilic nature of their molecules relative to those of Benz ions. The inorganic cations did not interfere due to the differences in their ionic size and hence their mobilities, polarities, and permeabilities as compared to those of Benz cation. The mechanism of selectivity is mainly based on the stereospecificity and electrostatic environment and depend on how much fitting is present between the locations of lipophilicity sites in the two competing species and bathing solution side and those present in the receptor of the ion-exchanger [33]. The data given in Table 4 revealed that, in most cases, the selectivity coefficients obtained for the coated silver sensors are lower than those for PVC membrane sensors, emphasizing the superiority of the former sensor in this respect as well [34-36].

Table 4 Selectivity coefficient values ($K^{\text{pot}}_{\text{BENZ},\text{Jz}^+}$) for BENZ sensors

Interferent	PVC sensors			CW sensors		
	Sensor 1	Sensor 2	Sensor 3	Sensor 4	Sensor 5	Sensor 6
K ⁺	8.91x10 ⁻⁴	2.09x10 ⁻³	1.58x10 ⁻⁴	1.21x10 ⁻⁴	8.91x10 ⁻⁴	1.20x10 ⁻⁴
NH ₄ ⁺	3.80x10 ⁻⁴	3.80x10 ⁻⁴	8.31x10 ⁻⁵	1.39x10 ⁻⁴	4.57x10 ⁻⁵	2.59x10 ⁻⁴
Li ⁺	2.63x10 ⁻³	4.07x10 ⁻⁴	3.98x10 ⁻⁴	3.55x10 ⁻⁴	1.09x10 ⁻⁴	1.20x10 ⁻⁴
Co ²⁺	5.37x10 ⁻³	4.47x10 ⁻⁴	5.62x10 ⁻³	3.71x10 ⁻³	1.70x10 ⁻³	2.24x10 ⁻²
Mg ²⁺	9.77x10 ⁻³	5.13x10 ⁻³	4.07x10 ⁻³	2.71x10 ⁻³	2.14x10 ⁻³	1.07x10 ⁻³
Fe ³⁺	3.31x10 ⁻³	9.80x10 ⁻³	4.04x10 ⁻³	1.70x10 ⁻³	1.15x10 ⁻³	2.17x10 ⁻³
Cu ²⁺	9.77x10 ⁻³	2.24x10 ⁻³	5.62x10 ⁻³	3.47x10 ⁻⁴	9.33x10 ⁻⁴	1.02x10 ⁻³
Ca ²⁺	1.25x10 ⁻²	5.13x10 ⁻³	9.77x10 ⁻³	1.70x10 ⁻³	1.99x10 ⁻³	1.15x10 ⁻³

Maltose	7.94×10^{-4}	7.41×10^{-4}	1.02×10^{-3}	1.76×10^{-4}	2.161×10^{-4}	8.31×10^{-4}
Lactose	5.89×10^{-4}	9.55×10^{-4}	1.23×10^{-3}	2.47×10^{-4}	5.25×10^{-4}	8.31×10^{-4}
Fructose	8.13×10^{-4}	9.55×10^{-4}	1.05×10^{-3}	4.51×10^{-4}	3.51×10^{-4}	9.12×10^{-4}
Glucose	9.58×10^{-4}	1.07×10^{-3}	1.23×10^{-3}	1.20×10^{-4}	1.04×10^{-4}	1.15×10^{-4}
Urea	7.94×10^{-4}	2.13×10^{-3}	1.45×10^{-3}	1.37×10^{-4}	9.12×10^{-4}	1.02×10^{-4}
β -alanine	7.32×10^{-3}	1.90×10^{-3}	1.10×10^{-3}	1.17×10^{-3}	8.13×10^{-4}	6.17×10^{-4}
Glycine	4.56×10^{-4}	8.51×10^{-4}	9.551×10^{-4}	1.17×10^{-4}	1.02×10^{-4}	2.23×10^{-3}
Ascorbic Acid	7.94×10^{-4}	8.13×10^{-4}	8.13×10^{-4}	2.55×10^{-4}	1.20×10^{-4}	1.29×10^{-4}

3.11 Effect of temperature

To study the effect of temperature on the response of the purposed sensors, the potential of 1.0×10^{-7} - 1.0×10^{-2} mol L⁻¹ Benz solutions were determined in different temperatures (20, 25, 30, 40, 50 and 60 °C) and calibration graphs were constructed, and the standard sensor potentials (E^oelec.) (Obtained from the calibration graphs) corresponding to each temperature was calculated. For the determination of the thermal coefficient (dE^o/dT) of the sensor, the standard sensor potential (E^oelec.) at different temperatures was plotted vs. (t – 25), where t is the temperature of the test solution. A straight-line plot was obtained according to the following equation [37].

$$E_o = E_o(25) + (dE_o / dT) (t - 25)$$

The values of the obtained thermal coefficient were found in the range 0.00054-0.00071 and 0.00019-0.0005 V^o/C for PVC and CW sensors, respectively. This indicates that the sensors have a high thermal stability within the investigated temperature range. The investigated sensors were found to be stable up to 60 °C without noticeable deviation from the Nernstian behavior.

3.12 Analytical applications

The optimized sensors under investigation have been successfully used for the potentiometric determination of Benz (pure form and pharmaceutical form) by using the standard addition and potentiometric titration methods. Represented potentiometric titration curves for sensor 5 and differential curves for sensor 3 are shown in Figs.7 and Fig.8, respectively and the results are summarized in Tables 5 and 6. In order to estimate the quality of the results, recovery values were also determined and are represented in the same tables. Determination of Benz in spiked urine and plasma samples was also carried at three different levels of concentration using the standard addition technique (Table 7). Those results showed that the proposed sensors have good efficiency in terms of sensitivity and can be used successfully for quality control of Benz drug in pure, pharmaceutical preparations, spiked urine and plasma samples. The results obtained from the standard addition method of the drug were compared with those obtained from the potentiometric titration method by applying F- and t-tests [38]. The results (Table 8), show that the calculated F- and t-values did not exceed the theoretical values, reflecting the accuracy and precision of the applied method.

For ruggedness of the method a comparison was performed between the intra- and inter-day assay results for Benz obtained by two M. Sc. students. The RSD values for the intra- and inter-day assays of Benz in the cited formulations performed in the same laboratory by the two analysts did not exceed 1.9 %. On the other hand, the robustness was examined while the parameter values (pH of the eluent and the laboratory temperature) were being deliberately slightly changed. Benz recovery percentages were good under most conditions, not showing any significant change when the critical parameters were modified.

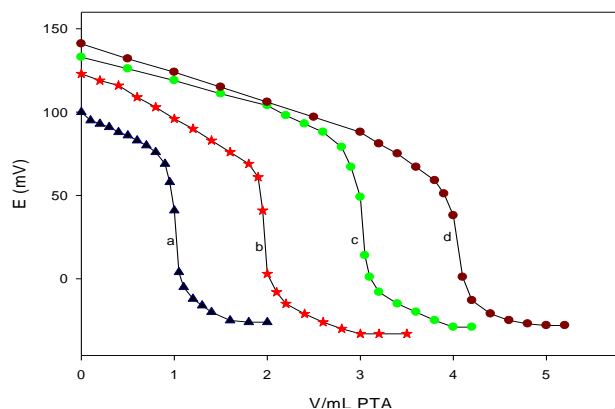


Fig. 7 Potentiometric titration curves of (a) 3, (b) 6, (c) 9 and (d) 12 mL of 10^{-2} mol L $^{-1}$ Benz using Benz-PTA CW sensor and 10^{-2} mol L $^{-1}$ PTA as titrant.

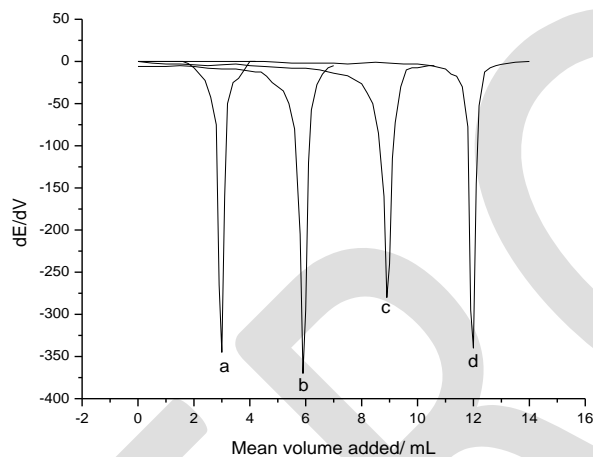


Fig. 8 Differential curves for potentiometric determination of (a) 3, (b) 6, (c) 9 and (d) 12 mL 10^{-2} mol L $^{-1}$ Benz using Benz-RN/0.3% NaTPB PVC sensor and 10^{-2} mol L $^{-1}$ NaTPB as titrant.

Table 5 Determination of Benz in pure form using the proposed sensors

Sensor type	Taken (mg)	Standard addition method		Taken (mg)	Potentiometric titration method	
		Recovery $\square\square\square$ SD	RSD (%) ^a		Recovery $\square\square\square$ SD	RSD (%) ^a
PVC sensors						
Sensor 1	3.46	99.0±1.73	1.75	10.38	98.30±1.46	1.48
	10.38	97.87±0.29	0.29	20.75	100.84±0.73	0.72
	17.29	97.03±.75	0.77	31.13	100.56±0.48	0.48
	24.21	99.47±1.33	1.34	41.51	101.04±0.36	0.36
Sensor 2	3.46	101.73±0.46	0.45	10.38	101.65±1.43	1.40
	10.38	98.21±.95	0.96	20.75	100.42±0.73	0.72
	17.29	96.97±0.57	0.59	31.13	97.89±0.38	0.39
	24.21	99.89±1.12	1.12	41.51	100.83±0.72	0.72
Sensor 3	3.46	98.49±1.76	1.79	10.38	97.85±0.79	0.80

10.38	97.61±1.23	1.26	20.75	98.9 ± 0.95	0.96
17.29	102.07±0.9	0.88	31.13	99.815±0.32	0.32
24.21	97.83±0.58	0.59	41.51	100.27±0.24	0.24

Coated-wire sensors

		PTA as titrant				
Sensor 4	3.46	99.73±.64	0.64	10.38	100.82±1.43	1.41
	10.38	99.11±0.90	0.91	20.75	99.17 ± 0.72	0.72
	17.29	99.8±0.81	0.82	31.13	100.28±0.48	0.48
	24.21	99.93±1.01	1.01	41.51	100.62±0.62	0.62
		PMA as titrant				
Sensor 5	3.46	101.4±0.53	0.52	10.38	98.31 ± 1.64	1.49
	10.38	100.93±1.48	1.47	20.75	100.89±0.72	0.72
	17.29	99.7±0.95	0.96	31.13	98.87 ± 0.96	0.98
	24.21	100.7±0.70	0.70	41.51	100.42±0.72	0.72
		NaTPB as titrant				
Sensor 6	3.46	100.33±1.33	1.32	10.38	100.53±0.46	0.46
	10.38	98.58±0.57	0.58	20.75	98.637±0.48	0.49
	17.29	96.33±1.27	1.32	31.13	100.37±0.32	0.32
	24.21	100.6±0.52	0.52	41.51	100.55±0.24	0.24

^a Mean of three determinations

Table 6 Determination of Benz in pharmaceutical formulation (TANTUM VERDE) using the proposed sensors

Sensor type	Taken (mg)	Standard addition method		Taken (mg)	Potentiometric titration method	
		Recovery □□□□SD	RSD (%) ^a		Recovery □□□□SD	RSD (%) ^a
PVC sensors						
Sensor 1	3.46	100.17±1.89	1.89	10.38	102.06±0.71	0.7
	10.38	98.03±0.29	0.29	20.75	99.61±1.43	1.44
	17.29	97.47±0.75	0.77	31.13	99.72±1.27	1.28
	24.21	99.77±1.16	1.16	41.51	100.62±0.63	0.62
Sensor 2	3.46	101.47±0.46	0.46	10.38	99.43±0.98	0.99
	10.38	98.75±0.95	0.96	20.75	100.84±0.73	0.72
	17.29	97.13±0.42	0.43	31.13	98.67±1.2	1.22
	24.21	100.27±0.64	0.63	41.51	100.62±0.63	0.62
Sensor 3	3.46	99.23±0.74	0.74	10.38	99.13±1.44	1.46
	10.38	97.18±1.25	1.29	20.75	99.18±0.83	0.83
	17.29	100.73±1.55	1.54	31.13	100.01±0.56	0.56
	24.21	98.17±0.58	0.59	41.51	100.41±0.41	0.41
Coated-wire sensors						
Sensor 4					PTA as titrant	

	3.46	101.07±1.67	1.66	10.38	99.43±0.98	0.99
	10.38	99.42±0.50	0.51	20.75	99.59±1.44	1.45
	17.29	99.1±1.19	1.20	31.13	100.06±.76	0.76
	24.21	99.53±0.46	0.46	41.51	101.04±0.36	0.36
					PMA as titrant	
Sensor 5	3.46	100.7±0.70	0.70	10.38	98.59±1.3	1.31
	10.38	99.97±1.15	1.16	20.75	100.42±.73	0.72
	17.29	99.7±0.95	0.96	31.13	99.63±1.16	1.16
	24.21	100.33±0.75	0.75	41.51	101.59±0.59	0.58
					NaTPB as titrant	
Sensor 6	3.46	99.53±1.36	1.36	10.38	100.53±0.46	0.46
	10.38	99.48±1.09	1.10	20.75	98.63±0.48	0.49
	17.29	97.37±0.75	0.77	31.13	100.59±0.6	0.60
	24.21	100.9±0.52	0.51	41.51	100.84±0.45	0.44

^a Mean of three determinations

Table 7 Determination of Benz in biological fluids (plasma and urine).

Sensor type	Spiked human plasma			Spiked urine		
	Taken (mg)	Recovery □□□□SD	RSD (%) ^a	Taken (mg)	Recovery □□□□SD	RSD (%) ^a
PVC sensors						
Sensor 1	3.46	98.47±0.69	0.70	10.38	98.07±0.69	0.71
	10.4	100.87±1.61	1.60	20.75	100.53±1.24	1.23
	17.3	101.21±0.77	0.76	31.13	101.37±.68	0.67
	24.2	98.97±0.55	0.55	41.51	99.32±0.58	0.58
Sensor 2	3.46	101.25±0.78	0.78	10.38	100.92±0.2	0.20
	10.4	98.72±1.26	1.28	20.75	99.17±0.49	0.49
	17.3	98.52±0.50	0.51	31.13	98.99±0.71	0.72
	24.2	100.73±0.80	0.80	41.51	100.27±0.80	0.81
Sensor 3	3.46	96.69±0.94	0.98	10.38	97.41±1.23	1.15
	10.4	97.93±1.34	1.37	20.75	98.82±0.57	0.58
	17.3	98.8±0.52	0.53	31.13	99.87±0.81	0.81
	24.2	100.05±1.17	1.17	41.51	100.72±1.17	1.16
Coated-wire sensors						
Sensor 4	3.46	98.56±0.44	0.45	10.38	99.16±0.90	0.91
	10.4	100.13±1.53	1.53	20.75	100.58±1.33	1.32
	17.3	101.11±0.27	0.27	31.13	100.96±0.27	0.27
	24.2	99.5± 1.13	1.13	41.51	100.32±1.29	1.29
Sensor 5	3.46	101.57±0.58	0.57	10.38	101.23±0.58	0.57
	10.4	97.31±0.34	0.35	20.75	97.74±0.52	0.54
	17.3	102.17±0.46	0.45	31.13	101.83±0.90	0.89
	24.2	99.85±0.82	0.83	41.51	100.32±0.83	0.82
Sensor 6	3.46	101.92±0.21	0.21	10.38	101.43±0.64	0.63

10.4	99.87±1.24	1.24	20.75	99.70±0.95	0.96
17.3	100.22±0.84	0.84	31.13	99.33±0.69	0.69
24.2	102.1± 0.67	0.68	41.51	101.37±0.58	0.57

Table 8 Statistical comparison between the results of an analysis of a pharmaceutical preparation TANTUM VERDE applying the standard addition and potentiometric titration methods

Parameter	standard addition method	potentiometric titration method
Sensor 1		
Mean recovery (%) ±SD	98.86 ^a ±1.31	100.50 ^a ±1.13
F-ratio	1.34 (9.28) ^b	
t-test	1.90 (2.447) ^c	
Sensor 2		
Mean recovery (%) ±SD	99.41 ^a ±1.88	99.89 ^a ±1.02
F-ratio	3.39 (9.28) ^b	
t-test	0.45 (2.447) ^c	
Sensor 3		
Mean recovery (%) ±SD	98.83 ^a ±1.52	99.68 ^a ±0.63
F-ratio	1.52 (9.28) ^b	
t-test	1.04 (2.447) ^c	
Sensor 4		
Mean recovery (%) ±SD	99.78 ^a ±0.88	100.03 ^a ±0.72
F-ratio	1.47 (9.28) ^b	
t-test	0.44 (2.447) ^c	
Sensor 5		
Mean recovery (%) ±SD	100.18 ^a ±0.43	100.058 ^a ±1.27
F-ratio	8.49 (9.28) ^b	
t-test	0.18 (2.447) ^c	
Sensor 6		
Mean recovery (%) ±SD	99.32 ^a ±1.46	99.74 ^a ±1.56
F-ratio	1.15 (9.28) ^b	
t-test	0.39 (2.447) ^c	

a: Average of four determinations

b: Tabulated F-value at 95% confidence level

c: Tabulated t-value at 95% confidence level and six degrees of freedom

4 Conclusion

Two kinds of potentiometric (PVC and a silver-coated wire) sensors were constructed for determination of Benz and a comparison was made between them. The sensors show favorable performance characteristics with short response times (~5 s), wide pH range between 3-8 and 2-8 for PVC membrane and coated-wire sensors respectively, low detection limits of 7.0×10^{-6} mol L⁻¹ and 7.2×10^{-6} mol L⁻¹ over the concentration range from 7.0×10^{-6} to 1.0×10^{-2} mol L⁻¹ and 1.0×10^{-6} – 1.0×10^{-2} mol L⁻¹, for PVC membrane and coated-

wire sensors respectively. Clearly the coated-wire sensors show wider pH range , better selectivity and a lower detection limit. The sensors were effectively used for determination of Benz in pharmaceutical preparations.

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