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Carbon paste and PVC electrodes for the potentiometric determination of trimetazidine, amantadine and ranitidine

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ABSTRACT

Carbon paste and PVC electrodes were constructed for the potentiometric determination of trimetazidine(TRMZ), amantadine(AM) and ranitidine(RN). Different methods for electrode fabrication(including formation of the ion pair in situ, soaking of the electrode in the ion pair aqueous solution, in addition to the classical modification of the electrode matrix with the ion pair) are described for both CPE and PVC electrodes. The electrodes exhibit Nernstian slopes 30.26±1.79, 58.2±1.5 and 59.5±3.3 for CPE and 28.8±1.27, 60.5±0.65& 54.6±3.4 for PVC corresponding to TRMZ, AM and RN, respectively. Comprehensive investigation of the electrode matrix compositions for each drug takes place as well as the effect of pH, temperature and life span. CPE electrodes showed superpriority when compared with the PVC regarding the ease of fabrication and regeneration as well as the short response time and long life time. The proposed electrodes were successfully applied for the determination of the TRMZ, AM and RN in pure solutions and dosage forms with good accuracy and precision.

KEYWORDS

PVC membrane;
Carbon paste;
Trimetazidine;
Amantadine;
Ranitidine;
Pharmaceutical preparations.

INTRODUCTION

The widespread dosefication and/or adulteration of commercially available pharmaceutical preparations demand reliable method for drug quality control that are preferably selective, rapid and can be undertaken with simple equipment. Nevertheless, most of these methods involve several manipulation steps before the final result of the analysis, have poor selectivity or require expensive apparatus. This is in contrast to potentiometric methods using ion selective electrodes, which is now a well established method[1-5], when applied to the analysis of pharmaceutical products, can be considered to be advantageous due to their simplicity, short measurement time, low cost, adequate precision and accuracy, wide analytical range(usually more 5 decades), the ability to measure the activity of various drugs from the formulation matrix in colored or cloudy samples as well as nondestructive measurement of the analyt sample. This makes ISE potentiometry very attractive tools for pharmaceutical analysis.

For routine analysis, the symmetric configuration is generally preferred in which the sensing membrane comes in direct contact with two aqueous solutions, the internal with fixed ion activity and the external with the ion activity to be measured. Even though the symmetric ISEs have found a wide range of applications[6-13], they still have certain inherent limitations as they are mechanically complicated, difficult to be manufactured in small size, as well as the shorter life time due to the leaching

of the electroactive material into both the internal and external solutions.

The constant development of ISEs is leading to sensors which not only have better performance but are also of simpler and more reliable construction. To overcome the aforementioned difficulties in the membrane electrodes, a new kind of all solid-state electrodes sensors, were reported which refer to a type of ISEs in which the internal reference element is in direct contact with the electroactive membrane matrix and thus contain no aqueous solution[7,9,12-16]. Due mainly to the elimination of the internal reference solution, these electrodes will have certain advantageous such as their small size, lower cost of production, and ability to operate in higher pressure environment where the symmetric ISEs might be damaged. Examples of this sensor design include the coated-wire electrodes(CWE), coated graphite electrodes as will as the conductive support electrodes. One disturbing drawback of these electrodes is the drift in the potential depending on the plasticizer content in the membrane matrix, the formation of a thin water film between the membrane and metal substrate makes these electrodes sensitive to the pH of solution and finally the poor adhesion of the active membrane to the metal substrate.

Nearly a half of century, carbon pastes made of carbon powder and a liquid binder belong among the most popular materials for preparation of various electrodes and sensors. Although considerable attention has been given to the preparation of CPEs, their applications in analytical chemistry[17,18] have mainly been based on selective preconcentration followed by voltammetric determination of various species, and just a few of these electrodes have been used as an ion selective electrode modified with the ion pair of the species under investigation[19-23]. When compared with similar PVC sensors, CPEs had the advantages of very low Ohmic resistance, the very short response time[24] in addition to the ease of fabrication and regeneration.

Trimetazidine(TRMZ); 1-[(2,3,4-trimethoxyphenyl) methyl] piperazine dihydrochloride is a clinically effective antianginal agent that has been used in the prophylaxis and management of angina pectoris, and in ischemia of neurosensorial tissues as in Meniere's disease[25]. Trimetazidine exhibits some cytoprotective effects on myocardial energy metabolism and exerts an antianginal effect in the absence of significant hemodynamic effects[26]. For these clinical successes, TRMZ has become unique among the antianginal agents, and it has been clinically used throughout many countries worldwide. Amantadine hydrochloride(Am-HCl)(tricyclo [3.3.1.1]decan-1-amine, hydrochloride) is reported[27] as a synthetic antiviral agent that inhibits the penetration and the replication of the virus, and recently used for bird-flow treatment in Egypt. Ranitidine(N-(2-{[5-dimethylamino-methyl]-2-furanil}-methyl thioethyl) N-methyl-nitro-1,1-diamino ethane) was introduced in the market in 1981 and is now extensively used in the treatment of duodenal and gastric ulceration, reflux oesophagitis and dyspepsia[28-29].

In spite of contentious progress in the design of highly selective electrodes for various ions, there has not been any report on the development of selective and sensitive TRMZ sensors, and no CPE were used for the determination of either AM or RN. The success in the application of CPEs for the potentiometric determination of metformin[22] was tested for determination of other cationic drug species such as TRMZ, AM and RN. In the present work, two types of ion selective electrodes with different methods of preparation were constructed and their performance characteristics were studied. The electrodes(PVC and CP) are based on incorporation of TRMZ, AM and RN-TPB ion pairs in the electrode matrixes or incorporation of ion pairing agents(such as sodium tetrakis(4-fluorophenyl) borate NaTFTPB or dodeca tungestophosphoric acid TPA) as well as soaking of the plan electrodes in the aqueous solution of drugs-TPB ion pairs. The present methods have the advantageous of simplicity, not time consuming and longer life time.

EXPERIMENTAL

Apparatus

All potential measurements were performed using a 692-pH meter(Metrohm), equipped with a sensing drug ion-selective electrode in conjugation with silver-silver chloride double junction reference electrode (Metrohm 6.0726.100). A combined pH glass electrode model 6.0202.100 was used for all pH measurements. Manual potentiometric titrations were performed

using a brand digital burette. The response time of the electrode was measured using 46-Range Digital Multimeter with PC interface. An Haake thermosetting circulating water bath with temperature stability of 25±1^{0}C.

Materials

1. Authentic samples

Trimetazidine dihydrochloride($C_{14}H_{22}N_2O_3$.2HCl, M.W. 339.3g/mol) sample was supplied by the(Global Napi Pharmaceuticals, Egypt), pure grade Am-HCl ($C_{10}H_{17}N$. HCl, Mwt 187.7) was provided by (Rameda Co. Egypt) and ranitidine HC1($C_{13}H_{22}N_4O_3S$,HCl, Mwt 350.9) was obtained from(Glaxo Wellcome Egypt S.A.E. El-Salam City-Cairo- A.R.E.). Stock drug solutions(0.1M) was prepared by dissolving an appropriate weight of each drug in water and completed to the mark in a 100ml calibrated flask with water.The contents of TRMZ, Am, RN were assigned to be 99.5, 99.67 and 99.84% using the officinal method[30]. The working standard solutions were obtained by further dilution of stock solution with water.

2. Pharmaceutical preparations

Metacardia® tablets(Global Napi Pharmaceuticals, Egypt) are labeled to contain 20mg of trimetazidine dihydrochloride per tablet, were purchased from local drug stores. Ten tablets of the drug formulations were weighed and finely powdered in a small dish and dissolved in the minimum volume of bidistilled water and filtered into a 100ml calibrated flask and assigned to be 98.88%. The pharmaceutical preparation(Adamine capsule, 100 mg amantadine per capsule) was used as amantadine sample, where 8 capsules were weighed and an accurately weighed portion of the powder, equivalent to one capsule was dissolved in 50ml water giving 2mg/ml amantadine hydrochloride which was assayed to be 100.20%. Zantac tablets,(Glaxo Wellcome Egypt S.A.E. El-Salam City-Cairo- A.R.E.) labeled to contain 150mg per tablet, Ranitidol® tablets (El. Nasr Pharmaceutical Chemicals Co., Abu-Zaabal, Egypt, 150mg), were used as samples. The contents of five tablets of the drug formulations were weighed and finely powdered in a small dish, amount equivalent to one tablet was dissolved in the minimum volume of water and filtered into a 100ml calibrated flask and analyzed according to the official methods with purity of 99.92, 99.53%, respectively.

3. Reagents

All the chemicals were of the analytical reagent grade and double distilled water was used throughout the experiments. Poly(vinyl chloride)(PVC)(Aldrich), Tetrahydrofuran(BDH) and o-nitrophenyl octyl ether oNPOE(Sigma) as a plasticizer, were used for the membrane preparation. Graphite powder(Aldrich 1-2μm) was used for preparation of the carbon paste electrode preparation with oNPOE as a plasticizer.

Standard solutions

Sodium tetraphenylborate(NaTPB) solution (ca.0.01M) was prepared by dissolving a weighed amount of the substance(Fluka) in worm water, then adjusted to pH 9 by adding sodium hydroxide solution and completed to the desired volume with water. The resulting solution was standardized potentiometrically against standard 0.01M thallium(I) nitrate solution[31]. Ion pairing agents; NaTPB, NaTFTPB, dodeca tungstophosphoric(PTA) and molybdophosphoric acid(MPA) were using analytical grad reagents.

Electrode construction

1. Ion pair preparation

The ion pairs of drugs with different ion pairing agents were prepared by drop wise addition of 0.01 M of TPB, PTA or MPA to 50ml of 0.01M drug solution with continuous stirring. The resulting precipitates were filtered, washed several times with distilled water and then dried at 50^{0}C. The resulting ion pair was washed with petroleum ether and kept dry in a dissector and analyzed with elemental analysis.

2. Sensor fabrication

Matrixes composition for both the PVC and carbon paste electrodes is given in reference 22. The prepared PVC electrodes were filled with 0.01M KCl and 0.01M drug solution using Ag/AgCl as internal reference electrode followed by soaking the electrodes were soaked in 0.01M of drug under the investigation for 24h before using. The modified PVC by soaking was prepared in the same manner using the plain electrode matrix(without any modification) where the electrode was soaked in the suspended solution of drug-TPB ion pair for 24hr before measurement. CPEs were pre-

pared by intimate mixing of graphite powder, modifier and pasting liquid in an agate mortar and the result paste was used to fill the electrode body[32] and the electrode was soaked 10^{-3}M of the drug solution. Unmodified CPE was soaked in the suspended solution of the ion pair for 24hr before measurement. Regeneration of the electrode was obtained by screwing the piston while holding the electrode surface against a flat solid support, polishing with a very smooth paper.

Analytical procedure

1. Electrode calibration

The electrodes were calibrated by transferring 25ml of 10^{-7}-10^{-1}M drug solutions into a 50ml double jacket thermostated glass cell at 25°C followed by immersing the ISE for each drug in conjugation with Ag/AgCl double junction reference electrode in the drug solution. The potential readings were recorded and plotted against drug concentration in logarithmic scale(-log[D]). The sensors performances were evaluated according to IUPAC recommendation[33].

2. Electrode response time

The dynamic response time of the electrode was tested by measuring the time required to achieve a steady state potential(within±1mV) after successive immersion of the electrode in a series of drug solutions, each having a 10-fold increase in concentration from 1.0×10^{-5} to 1.0×10^{-1}M.

3. Effect of pH

The influence of pH on the response of both PVC and CPE was checked by recording the potential readings of the cell for solutions containing 10^{-2}M of each drug at different pH values(pH 3-11). Variation of pH value was done by adding very small volumes of HCl and/or NaOH solution(0.1-1M of each) to 20ml of the drug solution.

4. Effect of temperature

To study the thermal stability of the electrode, calibration plots were constructed at different temperatures ranging 25-70°C. The standard cell potentials(E^0cell) were determined at each temperature from the respective calibration plots as the intercepts of these plots at pD=0, and plotted versus(T-25), where T is the absolute temperature of the solution. A straight-line plot is obtained where the slope represents the isothermal coefficient of the electrode according to the following equation[34,35]:

$$E^0_{cell} = E^0_{cell(25^oC)} + (dE^0/dt)_{cell}(t-25)$$

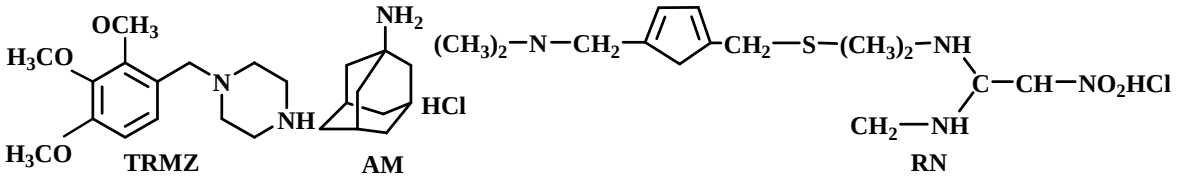
Potentiometric titration

Aliquots of the RN containing(17.5-52.5mg for pure solution or 7.5-22.5mg of tablet samples) or AM solution(2-20mg) were pipetted into a 50ml beaker, and the volume was completed to 25ml with water. NaTPB was used as a titrant and the titration process was monitored potentiometrically using the RN or AM ISEs. The potential readings were plotted against the ml added from the titrant to estimate the end point from the S shape titration curve or using the first & second derivative of curve. For TRMZ, an excess(10ml of 0.01M TPB) was added to the sample solution containing 10-35mg where the un-reacted amounts of TPB were back titrated with Tl^+ using unmodified carbon paste electrode[31].

RESULTS AND DISCUSSION

Sensor performance

The most traditional way in preparation of sensors for cationic drug species is the incorporation of the ion in question, usually in the form of an ion-pair[1-5] with some anionic ion pairing such as NaTPB, TPA, TSA, flavianate, reineckate or MPA as counter-anion in the electrode matrix. The drug under investigation present in the cationic form which contain nitrogen atom that can form an ion pairs with different ion pairing agents.



TRMZ AM RN

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In the present work, the ion pairs of the drug under investigation with NaTPB, TPA, TSA or MPA were precipitated and the chemical formulas of these ion pairs were estimated with elemental analysis. It was found that RN and AM form ion association with TPB with the chemical formula of $C_{37}H_{42}SN_4B$ and $C_{34}H_{27}NB$ indicating the formation of 1:1 ion pair, while TRMZ gave $C_{62}H_{62}N_2B$ which indicate the formation of 1:2 ion pair. The ion pairs with TPA, TSA or MPA did not follow the 1:1 ratio and have a limited solubility in the matrix composition, so it will not be used.

In addition to the traditional method for electrode matrix preparation, some different techniques for the electrode fabrication include the incorporation of a suitable ion pairing agents into the electrode matrix, followed by soaking the electrode in the aqueous drug solution led to the formation of the ion pair on the electrode surface which will be consequently extracted into the electrode matrix(plasticizer) so the electrode become gradually saturated with the ion pair. Also, it is expected that during the soaking of the plan electrode in the aqueous suspended ion pair solution, the organic solvent(plasticizer) will extract the ion pair and become gradually saturated with the ion pair[36,37].

Preliminary experiment showed that both the PVC and CPEs prepared using oNPOE as a plasticizer and contain no electroactive material had no response towards the drugs under investigation, while the PVC and CP matrixes modified with different methods showed Nernstain responses towards drugs with different slopes and sensitivity depend on the drug under investigation and the method for fabrication(TABLE 1 and figure 1).

For TRMZ, data obtained show the superiority of the modification with the ion pair method over the in situ or soaking methods indicated by the highest slope with lower detection limit. In case of the RN and AM, the modification of the electrode in situ was better than other listed methods. The lower limit of detection(LOD) of the electrode is defined as the concentration range of PD

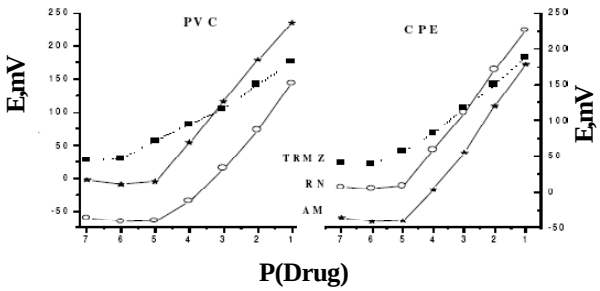

Figure 1: Calibration graphs of different drugs using CPE and PVC electrodes with the optimum matrix composition

TABLE 1: Performance characteristics* of different crugs PVC and carbon paste electrodes fabricated with different techniques.

Drug	Electrode	Code	Parameter							
			Fabrication technique	Linear range, M	Intercept, mV	Slope**, mV/decade	r	DL, M	Response time, sec	Life span, day
TRMZ	PVC	1	Modified	10^{-6}-10^{-1}	199.5±4.9	28.8±1.27	0.99616	9×10^{-7}	6	21
		2	In situ	10^{-5}-10^{-1}	214.3±5.5	33.1±1.7	0.99669	5×10^{-6}		
		3	Soaked	10^{-5}-10^{-1}	196.1±3.0	27.9±0.9	0.99839	6×10^{-6}		
	CPE	4	Modified	10^{-5}-10^{-1}	211.4±6.9	30.3±1.79	0.99307	6×10^{-7}	3	30
		5	In situ	10^{-5}-10^{-1}	169.9±2.0	28.9±0.6	0.99936	7×10^{-6}		
		6	Soaked	10^{-5}-10^{-1}	234.6±1.4	31.6±0.4	0.99974	6×10^{-6}		
RN	PVC	7	Modified	10^{-4}-10^{-1}	185±9.7	55±3.8	0.99415	10^{-4}		
		8	In situ	10^{-5}-10^{-1}	184±14.7	54.6±3.4	0.99527	10^{-5}	5	28
		9	Soaked	10^{-4}-10^{-1}	196±10.4	51.1±3.5	0.99606	10^{-4}		
	CPE	10	Modified	10^{-4}-10^{-1}	105.5±5.3	51.7±1.94	0.99736	5×10^{-5}		
		11	In situ	10^{-5}-10^{-1}	279.0±3.5	59.5±3.3	0.99944	6×10^{-6}	2	60
		12	Soaked	10^{-4}-10^{-1}	227±3.5	48.2±1.29	0.99885	3×10^{-5}		
AM	PVC	13	Modified	10^{-5}-10^{-1}	315.8±6.9	58.8±2.8	0.9981	10^{-5}		
		14	In situ	10^{-5}-10^{-1}	298.1±2.1	60.5±0.65	0.99983	6×10^{-6}	5	28
		15	Soaked	10^{-5}-10^{-1}	307±11.6	54.3±3.5	0.99379	10^{-5}		
	CPE	19	Modified	10^{-4}-10^{-1}	149±10.2	52.7±3.7	0.99506	10^{-4}		
		17	In situ	10^{-5}-10^{-1}	160.4±5.2	58.2±1.5	0.9989	4×10^{-6}	1.6	60
		18	Soaked	10^{-4}-10^{-1}	224.9±7.3	46.3±2.2	0.99556	10^{-4}		

***Results are average of five different calibrations, **Values are calculated according to IUPA recommendation**

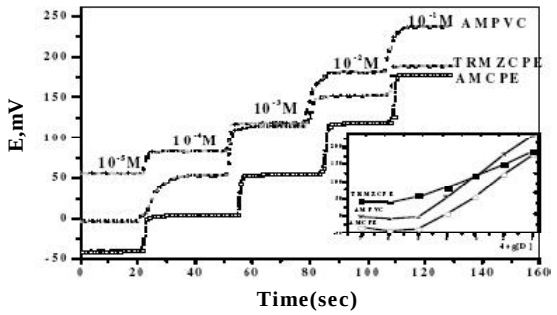

Figure 2: Dynamic responses for PVC and CP electrodes of different drugs.

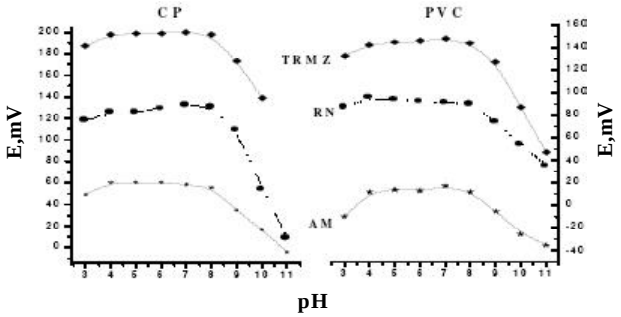

Figure 3: Effect of pH on the potential readings of PVC and CPEs of different drugs(0.01M concentration of each drug)

corresponding to the intersection of the two extrapolated linear segments of the calibration graph, equals to 9.3×10^{-7}, 6×10^{-7}, 10^{-5}, 6.1×10^{-6}, 6.3×10^{-6} and 4.410^{-6} M for TRMZ, AM and RN PVC & CPEs, respectively.

Response time

The response time of PVC and CPEs under the optimum condition for each drug was measured according IUPAC recommendation(TABLE 1 and figure 2). The responses for AMCPEs were spontaneous as the response time was found to be 1.6 s for concentration of $\geq1\times10^{-2}$M and 3s for lower concentrations; this very short response time can be explained by the fact that the carbon paste consists of carbon powder each is surrounded by a very thin film of NPOE and carbon particle itself acts as a conductor[38]. For PVC electrodes, the corresponding response time was 5 and 8 second respectively. The longer response time of the PVC membrane electrodes may be due to their configuration with an internal reference solution. For TRMZ and RN, CPEs showed response time of 2, 3 sec for concentration $\geq1\times10^{-2}$M while the PVC gave 5, 6 sec for the same concentration.

Effect of the pH

The influence of pH on the response of both PVC membrane and CPE was checked for the three drugs under investigation. The plots of E(mV) versus pH(figure 3) indicate that the response of the electrodes was pH independent in the pH ranges: 4.0-8.0 for PVC and CP for TRMZ and RN. In the case of AM, the working pH range was from 4-9 and 4-8 for PVC and CP, respectively. Calibration graphs of the ISEs at different pH values indicated the highest slope of the calibration graph was at pH 5 for PVC and 6 for CPE. Using of acetate buffer at the mentioned optimum pH value did not improve the slope of the calibration graph so the measurements were done in the aqueous solution. At the lower pH values the potential readings decrease; this may be attributed to the penetration of chloride ion in the electrode gel layer.

Effect of temperature

Calibration of different drugs using either PVC or CPEs were done at different temperatures ranging between 25-70^{0}C. Results show that the calibration graphs of the PVC electrodes have very stable slopes in the temperature range 25-60^{0}C while the CPEs show stable slope of the calibration graph in the temperature range 30-50^{0}C. The isothermal coefficients of both PVC membranes were calculated for different drugs and have values 0.000415, 0.00055, 0.001V/^{0}C for AM, RN and TRMZ respectively. The corresponding values for CPEs were -0.00334, -0.004 and -0.009V/^{0}C for the drugs in the same order. In general, the carbon paste electrodes showed higher sensitivity to the change in the temperature of the solution as major types of solid electrodes without internal reference solution[19,38] while the PVC electrode which contains an internal reference solution did not suffer from this sensitivity. The relative sensitivity of CP towards the change in the temperature may be also due to the change in the conductivity of the electrode with increasing the temperature, which will affect the potential readings, the isothermal coefficient of the blank electrode was 0.00215V/^{0}C.

Potential drift

Day-to-day calibration was done using both PVC and CPEs to evaluate the useful lifetime of both electrodes. Both AM and RN, PVC electrodes show a use-

ful lifetime of 4 weeks, during which the potential slope is reproducible to within ±1mV/decade. Carbon paste electrodes prepared with in situ mode have a relative lifetime as the electrode show a stable slope(±1mV/decade) from 1-60 days after preparation. Regarding TRMZ ISEs, PVC and CPEs modified with the ion pairs showed useful life time of 3 and 4 weeks respectively. In general, the master PVC membranes for each drug were stable at 4^0C for 3 months during which a new membrane electrode can be fabricated. To obtain a new CPE, regeneration can be done by squeezing out a small amount of the paste, and polishing the electrode on a smooth filter paper till obtaining a shiny surface, which offer a new fresh electrode surface for measurement[32].

Potentiometric titration

In contrast to direct potentiometric measurements requiring careful calibrations of measuring cells, the potentiometric titration techniques offers the advantage of high accuracy and precision; although the cost of increased time and increased consumption of reagents used as titrants.

Different electrodes listed in TABLE 1 were used in the potentiometric titration of different drugs with TPB. In the case of AM and AM, the CPEs modified with the ion pairs in situ showed the highest potential break at the end point as well as higher total potential change. Different titrants were tested in the potentiometric titration of both drugs, and using of TPB as a titrant gave the best titration curve with the highest potential break at the end point and a well defined reaction sticiochiometry(1:1). Other titrants(TPA, MPA) gave a poor titration curve with undefined reaction stiocheometry(1:3, 1:4). The titration curves were symmetrical with a very well defined potential jump indicating the high sensitivity of the electrode(figure 4). The average recoveries for titration of 2-10mg AM and 17.5-52.5mg RN was 99.67 and 99.84% respectively with standard deviations of 1.9, 2.2%. Titration of 6 mg AM gave average recovery of 99.8% with a relative RDS of 1.6%(n=10), while titration of 35.5mg RN gave an average recovery of 100.5±1.4%(n=10).

With TRMZ, the titration curves using different electrodes showed different potential break at the end point depending on the type of the electrode and titrant and CPE modified with the ion pair gave the best results. Generally, the potential break and the total potential change of the titration curves of TRMZ are not as high as that in case of AM and RN(TRMZ are doubly charged and the slope of the calibration curves was 30.26mV per decade) which lower the total potential change of the titration curve. To obtain more reproducible titration curves, a known volume of TPB was added to the drug solution and the excess of TPB was titrated with Tl^+ or CPC as a back titrant. Even a higher dE/dv was obtained using CPC as a back titrant, the results obtained with Tl^+ was more reproducible with better recovery. The equivalent volume of the titrant(Tl^+) decreased with increasing the TRMZ concentration from 10-35mg indicating consuming of TPB due to the formation of TRMA-$(TPB)_2$ ion pair. The average recoveries for titration of 10-35mg TRMZ was 101.35± 3.8%. Titration of 20mg TRMZ gave average recovery of 96.3±4.3%(n=10).

Analytical application

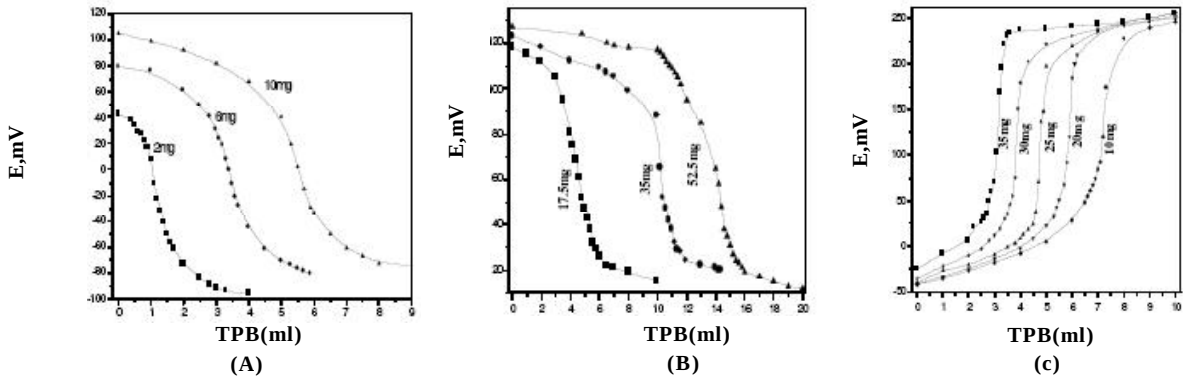

Figure 4: Potentiometric tiration of different drugs, (a), (b): AM and RN with 10^{-2}M Na-TPB using carbon paste electrode modified with KTFTPB and (c) back titration of TRMZ using unmodified CPE with 0^{-2}M Tl

TABLE 2: Determination of TRMZ, RN and AM in pure solutions and pharmaceutical preparation by potentiometric titration using carbon paste electrode modified with NaTFTPB

Drug	Sample	Taken, mg	Found, mg		Recovery(%)*	RSD
			Official	ISE		
Amantadine	Pure solution	2	1.98	2.03	102.6	1.6
		6	5.99	5.95	99.4	2.3
		10	10.02	9.91	98.9	1.8
	Adamine 100mg	2	1.99	2.02	101.7	1.6
		6	6.08	6.38	104.9	2.3
		10	10.06	9.96	99.0	1.6
		20	19.88	19.66	98.9	1.8
Ranitidine	Pure solution	17.5	17.38	17.12	98.5	2.3
		35	35.05	35.79	102.1	2.5
		52.5	51.90	51.33	98.9	1.8
	Zantac 150mg	7.5	7.49	7.55	100.8	0.8
		15.0	15.02	14.78	98.4	1.9
		22.5	22.48	22.37	99.5	1.2
	Ranitidine 100mg	7.5	7.46	7.83	104.9	3.4
		15	14.77	14.65	99.2	1.3
		22.5	22.53	22.46	99.7	1.8
Trimetazidine	Pure solution	10	9.80	10.45	106.6	3.5
		20	20.10	19.36	96.3	4.3
		25	25.03	25.43	101.6	1.5
		30	29.88	30.57	102.3	2.4
		35	35.07	33.91	96.7	3.7
	Metacardia 20mg	4	3.95	4.17	105.6	2.9
		8	8.08	8.24	102.0	1.7

***Mean recovery and standard deviations for five determinations**

The versatility of the method has been investigated by measuring TRMZ, RN or AM concentration in either pure authentic solutions or real pharmaceutical formulations with comparing the results with the standard methods[30]. Pharmaceutical diluents commonly used in drug formulations(e.g., glucose, lactose, starch, mannitol ….) at concentration as high as 20 fold molar excess over active ingredient may interfere in the for drug quality control depending on the method of assy. In the present work applying both PVC and CPEs, this filler or diluents did not show a significant interference on the potentiometric titration.

Results obtained(TABLE 2) showed the possibility of applying the fabricated sensors in the determination of different drugs with recoveries which are in agreement with those obtained from the British Pharmacopoeia.

CONCLUSION

The present work was aimed to investigate the application of novel sensor(either CPEs or PVC membranes) for the potentiometric determination of TRMZ, RN and AM. The incorporation of the ion pairing reagent(in situ mode) gave better results than other methods of preparation allowing the determination of many drugs those gave a suspended or oily stick ion pairs with the reduction of the time required for electrode fabrication. CPEs show superior life time and response time than the PVC electrodes with the ease of fabrication and regeneration technique. CPEs showed similar sensitivity (and in some cases more sensitive) compared with PVC electrodes and to the electrodes previously published for the potentiometric determination of RN[6,8,10,12,15-16] or AM[7,9,13]. The proposed electrodes can be successfully used in assaying of different drugs in the pharmaceutical preparation with good accuracy. More comprehensive studies will be done for comparison of the suitability of PVC and CPEs in the flow injection determination of these drugs as well as determination of selectivity coefficients in both the batch and FIA mode.

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