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ORIGINAL PAPER

Novel potentiometric sensors for the selective determination of domperidone

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Abstract The fabrication and electrochemical response characteristics of two novel potentiometric sensors for the selective determination of domperidone (DOM) are described. The two fabricated sensors incorporate DOM–PTA (phosphotungstic acid) ion pair as the electroactive material. The sensors include a PVC membrane sensor and a carbon paste sensor. The sensors showed a linear, stable, and near Nernstian slope of 56.5 and 57.8 mV/decade for PVC membrane and carbon paste sensors, respectively over a relatively wide range of DOM concentration (1.0×10^{-1}–1.0×10^{-5} and 1.0×10^{-1}–3.55×10^{-6} M). The response time of DOM–PTA membrane sensor was less than 25 s and that in the case of carbon paste sensor was less than 20 s. A useful pH range of 4–6 was obtained for both types of sensors. A detection limit of 7.36×10^{-5} M was obtained for PVC membrane sensor and 1.0×10^{-6} M was obtained for carbon paste sensor. The proposed sensors showed very good selectivity to DOM in the presence of a large number of other interfering ions. The analytical application of the developed sensors in the determination of the drug in pharmaceutical formulations such as tablets was investigated. The results obtained are in good agreement with the values obtained by the standard method. The sensors were also applied for the determination of DOM in real samples such as urine by the standard addition method.

Keywords Domperidone · Potentiometry · Polymeric membrane sensor · Carbon paste sensor · Pharmaceutical formulations · Urine sample

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1 Introduction

Domperidone, 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl) propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one, is a white or almost white powder [1] (Fig. 1). It is a dopamine antagonist used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies. Domperidone is indicated for treating symptoms associated with upper gastrointestinal motility disorders caused by chronic and sub acute gastritis. It is a gastrointestinal emptying adjunct, a peristaltic stimulant, and also exhibits antiemetic properties. Domperidone is also used to prevent stomach problems associated with the use of certain medications used to treat Parkinson's disease.

Domperidone is a drug that has a side effect of increasing milk production, probably by increasing prolactin production by the pituitary gland. Domperidone is excreted in breast milk, and no studies on its effects on breast feeding infants have been reported in the literature. Individual incidents of problems with the drug include cardiac arrest and arrhythmia, complications with other medications, as well as complications with improper intravenous use.

The pharmacokinetics and bioavailability in man have been studied with domperidone levels measured by a radioimmunoassay (RIA) method using antibodies raised in rabbits against domperidone [2]. Several other analytical methods reported for quantitative determination of domperidone include spectrophotometry [3–5], high performance liquid chromatography [6–11], anodic differential pulse voltammetry [12], and titrimetry [13]. However, most of these methods require expensive and sophisticated instruments and are time consuming. Hence it is worthwhile to develop a simple and sensitive method for the analysis of this drug.

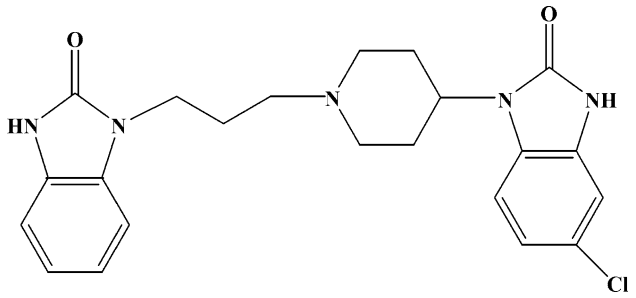

Fig. 1 Structure of domperidone

Potentiometric sensors have the advantages of low cost, ease of use, and maintenance, and also simplicity and speed of assay procedure. The reliability of the analytical information makes them very attractive for the assay of pharmaceutical products. Suitable Ion Selective Electrodes (ISEs) for drugs have enough selectivity towards the drugs over pharmaceutical excipients, and hence they can be used for the quantitative analysis of the drugs in pharmaceutical preparations without prior separations. In particular, ISEs are very useful in the case of drugs which are unstable during prior separation [14–16]. The high selectivity of these electrodes impart a great advantage over other techniques.

In continuation of our previous studies on drug analysis [17–22], an attempt has been made to develop two types of potentiometric sensors for the quantitative determination of DOM. The reported sensors include a plastic membrane sensor and a carbon paste sensor by incorporating the ion-pair DOM–PTA, and the performance characteristics were studied. The sensors were successfully applied for the determination of DOM in pure solutions and in pharmaceutical preparations, and the results obtained are in good agreement with those obtained by the official method. The sensors were also applied to the recovery of the drug from spiked urine samples.

2 Experimental

2.1 Reagents and materials

All chemicals used were of analytical grade. Phosphotungstic acid (PTA), Dibutyl sebacate (DBS) and all of the metal salts used were obtained from Merck. Bis(2-ethyl hexyl) phthalate (BEP), bis(2-ethyl hexyl) sebacate (BES), bis(2-ethyl hexyl) adipate (BEA), and di-*n*-butyl phthalate (DBP) were obtained from Lancaster (UK); tetrahydrofuran (THF) from local chemical suppliers (s.d.fine chem, India); and graphite powder (<150 micron) from Aldrich. Pure-grade DOM was obtained as a gift sample. Pharmaceutical preparations Vomihtop (Cipla, India) and Domitil (Bal Pharma, India) were purchased from local market.

2.2 Apparatus

All emf measurements were carried out using the following cell assembly. A saturated calomel electrode (SCE) was used as the external as well as the internal reference electrode. The electrochemical cell assembly may be represented as

2.2.1 For membrane sensor

Saturated calomel electrode | internal filling solution (1×10^{-1} M NaCl solution + 1×10^{-3} M drug solution) | PVC membrane | test solution | saturated calomel electrode.

2.2.2 For carbon paste sensor

Reference electrode | test solution | carbon paste electrode.

A Metrohm 781 ion meter was used for potential measurements. All emf measurements were carried out at 25 ± 1 °C.

2.3 Synthesis of the ion association

Ionophore is the electroactive component of a sensor. The DOM–PTA ion association was prepared by mixing 25 mL 10^{-2} M DOM with 25 mL 10^{-2} M PTA solutions. The mixture was then shaken well for 10 min, and the produced precipitate was filtered through a Whatman filter paper, washed thoroughly with distilled water, dried at room temperature, and stored in a desiccator. The composition of the ion association was confirmed by elemental analysis to be 1:1 (DOM:ion pairing reagent). The elemental analysis data obtained for the ion association is as follows:

DOM–PTA ion association
Found (%) C—7.85, H—0.89, N—2.23
Calculated (%) C—7.98, H—0.82, N—2.12

2.4 Fabrication of DOM membrane sensor

The membrane electrode was constructed according to the Craggs procedure [23]. A required amount of the ion pair, plasticizer, and PVC was dissolved in 5–7 mL of THF. The mixture was then poured into glass rings struck onto a glass plate. It was allowed to stand overnight for slow evaporation of solvent and formation of the sensing membrane. Small portions of the membrane was cut out and glued to one end of a hollow glass tube. The electrode body was filled with an inner filling solution containing NaCl (1.0×10^{-1} M) and DOM (1.0×10^{-3} M). The finished electrode was conditioned in DOM solution (1.0×10^{-3} M) for 24 h.

The electrode was washed with distilled water before measurement.

2.5 Fabrication of DOM carbon paste sensor

Weighed amount of the ion association (DOM–PTA) and high purity graphite were mixed together. To the homogenized mixture, a weighed amount of the plasticizer was added. The carbon paste thus obtained was then filled to one end of a teflon holder with a hole at one end for the carbon paste filling. Electrical contact was made with a copper rod that runs through the center of the electrode. Appropriate packing and smooth surface were achieved by polishing the surface of the sensor against a filter paper. The electrode surface could be easily regenerated by removing a small amount of the paste from the tip of the electrode. The sensor was conditioned by soaking it in a 1.0×10^{-3} M solution of DOM for 12 h.

2.6 Procedure

A 1.0×10^{-1} M solution of the drug was prepared in methanol in a 100 mL volumetric flask. The dilution series were prepared by serial dilution of the stock solution with distilled water in 50 mL volumetric flasks. The fabricated sensors were immersed in each of the different concentrations and performances of the electrodes were investigated by measuring the emf values between different concentrations of the respective DOM solutions. Calibration graph was obtained by plotting EMF (mV) versus log c. The resultant calibration graph was used for subsequent determination of unknown concentration of DOM.

2.7 Analysis of pharmaceutical formulation (tablets)

Ten tablets of each (Vomihtop and Domitil) were weighed, crushed, and ground into fine powder. An adequate amount of this powder, corresponding to the mass of one tablet was taken, dissolved in dilute methanol and filtered into a 100-mL volumetric flask and made upto volume. A volume of 10 mL of this solution was transferred to a 100-mL flask, and the solution was made upto the mark after adjusting the pH to 5. The presently developed sensors were directly immersed into 15 mL of the solution, and the potential response was noted. The potential obtained was used to evaluate the content of drug in the tablet from the calibration graph (potential versus log concentration).

2.8 Analysis of urine sample

The developed sensors were applied to the determination of DOM content in urine samples. Standard addition technique was used to evaluate the drug content. A volume of 20 mL of the urine sample containing DOM was taken in a beaker, and the potential reading was taken. It was then spiked with 2 mL of known concentration of the drug solution, and the potential value was determined again. The difference in the potential readings between the spiked and the unspiked samples was noted. From the difference, the amount of DOM present in the original unspiked sample was calculated [24].

3 Results and discussion

3.1 Optimization studies of the two types of sensors

The optimization of composition of the two types sensors were carried out by varying the nature and also the amount of the plasticizer and ionophore used. This is because the sensitivity of the electrode is dependent on the amount of the ion exchanger and also on the nature and amount of the plasticizer used. The addition of plasticizer influences selectivity, sensitivity, and the working range of the electrodes due to variation in free energy of interaction of electroactive ions and ionophore in polymer matrices.

In this study, five different plasticizers were employed to study their effects on the electrochemical behaviour of the membrane. The five different plasticizers used were BEP, BES, DBP, DBS, and BEA. The membrane composition was studied by varying the percentages of the ion pair, PVC, and plasticizer. The membrane compositions were varied until the optimum composition that exhibits the best performances was obtained. The potential responses of a set of 15 different sensors constructed with different plasticizers and different composition ratios are given in Table 1. The results revealed that the best composition was obtained for sensor D_{P8} with ion association:PVC:plasticizer (BEP) as 1.2:50.2:48.6 wt%. The slopes of the sensors varied from Nernstian values depending on the use of plasticizer, the proportion of the plasticizer with PVC, and of the electroactive compound. The PVC acts as a regular support matrix for the membrane but its use creates a need for a plasticizer [25]. In the investigation under this study, BEP was found to be the optimum available plasticizer for the PVC membrane sensor. It plasticizes the membrane, dissolves the ion association complexes, and adjusts both permittivity of the membrane and mobility of the ion-exchanger sites to give the highest possible selectivity and sensitivity [26]. The calibration plot of sensor D_{P8} with optimized composition is shown in Fig. 2. This sensor gave a linear response behavior within the concentration range 1.0×10^{-1}–1.0×10^{-5} M of DOM with a slope of 56.5 mV/decade and a lower detection limit of 7.36×10^{-5} M.

Table 1 Optimization of composition of PVC membrane sensor using DOM–PTA ion association

Sensor	Composition % (w/w)			Slope (mV/decade)
	Ion pair	PVC	Plasticizer	
D_{P1}	1.0	42.4	56.6, DBP	50.8
D_{P2}	1.2	50.2	48.6, DBP	49.3
D_{P3}	1.4	32.6	66.0, DBP	52.4
D_{P4}	1.0	42.4	56.6, BES	48.5
D_{P5}	1.2	50.2	48.6, BES	49.2
D_{P6}	1.4	32.6	66.0, BES	43.1
D_{P7}	1.0	42.4	56.6, BEP	52.3
D_{P8}	*1.2*	*50.2*	*48.6, BEP*	*56.5*
D_{P9}	1.4	32.6	66.0, BEP	49.2
D_{P10}	1.0	42.4	56.6, DBS	48.3
D_{P11}	1.2	50.2	48.6, DBS	50.9
D_{P12}	1.4	32.6	66.0, DBS	49.8
D_{P13}	1.0	42.4	56.6, BEA	47.6
D_{P14}	1.2	50.2	48.6, BEA	47.8
D_{P15}	1.4	32.6	66.0, BEA	51.8

Table 2 Optimization of composition of carbon paste sensor using DOM–PTA ion association

Sensor	Composition % (w/w)			Slope (mV/decade)
	Ion pair	Graphite	Plasticizer	
D_{C1}	2.0	33.0	65.0, BEP	48.9
D_{C2}	2.2	40.2	57.6, BEP	52.4
D_{C3}	2.4	42.0	55.6, BEP	51.6
D_{C4}	2.0	33.0	65.0, DBP	50.4
D_{C5}	*2.2*	*40.2*	*57.6, DBP*	*57.8*
D_{C6}	2.4	42.0	55.6, DBP	51.4
D_{C7}	2.0	33.0	65.0, DBS	49.5
D_{C8}	2.2	40.2	57.6, DBS	43.6
D_{C9}	2.4	42.0	55.6, DBS	45.2
D_{C10}	2.0	33.0	65.0, BES	39.8
D_{C11}	2.2	40.2	57.6, BES	48.3
D_{C12}	2.4	42.0	55.6, BES	49.6
D_{C13}	2.0	33.0	65.0, BEA	50.7
D_{C14}	2.2	40.2	57.6, BEA	49.3
D_{C15}	2.4	42.0	55.6, BEA	49.2

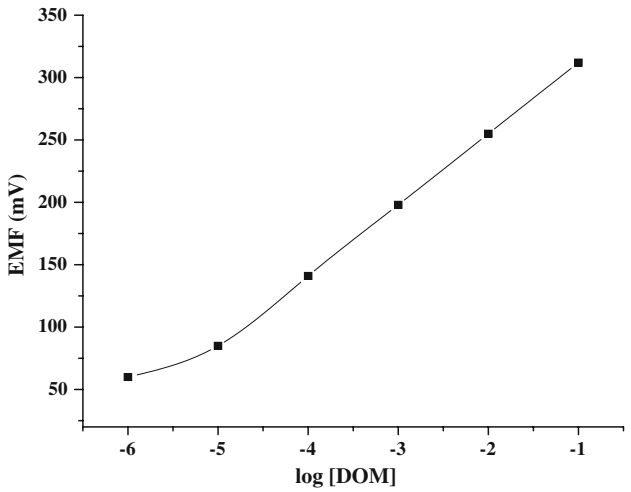

Fig. 2 Calibration graph for DOM selective PVC membrane sensor based on DOM–PTA ion association (D_{P8})

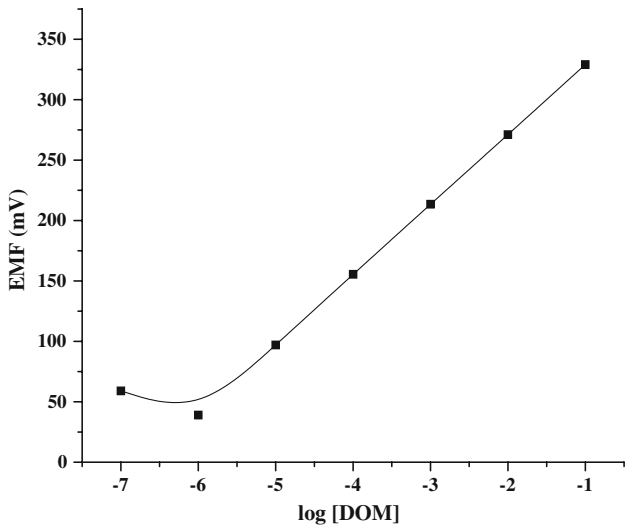

Fig. 3 Calibration graph for DOM selective carbon paste sensor based on DOM–PTA ion association (Dc_5)

The composition of the carbon paste ingredients were also varied to get the best response and are consolidated in Table 2. The optimized composition in the case of this sensor may be represented as 2.2:40.2:57.6 wt% (ionophore:graphite:plasticizer) (D_{C5}). All the five plasticizers which were tried for membrane sensors have been tried in the case of carbon paste sensors also. The use of DBP resulted in a Nernstian linear plot over the concentration range 1.0×10^{-1}–3.55×10^{-6} M (Fig. 3). The results showed that the sensor D_{C5}, made of 2.2% DOM–PTA ion pair exhibits the best performance (slope 57.8 mV/decade, detection limit 1.0×10^{-6} M).

The response characteristics of the two types of sensors under investigation are summarized in Table 3.

3.2 Surface morphology study of the developed membrane

SEM analysis was conducted to study the surface morphology of the developed D_{P8} membrane. Figure 4 gives the SEM image for D_{P8} membrane. The extend of homogeneity of a membrane surface is clearly visible in the SEM image. A homogeneous membrane is found to exhibit good

Table 3 Response characteristics of the developed sensors D_{P8} and Dc_5

Parameter	PVC membrane sensor D_{P8}	Carbon paste sensor Dc_5
Slope (mV/decade)	56.5	57.8
Linear range (M)	1.0×10^{-1}–1.0×10^{-5}	1.0×10^{-1}–3.55×10^{-6}
pH range	4–6	4–6
Detection limit (M)	7.36×10^{-5}	1.00×10^{-6}
Response time (s)	<25	<20
Shelf life	3 weeks	2 weeks

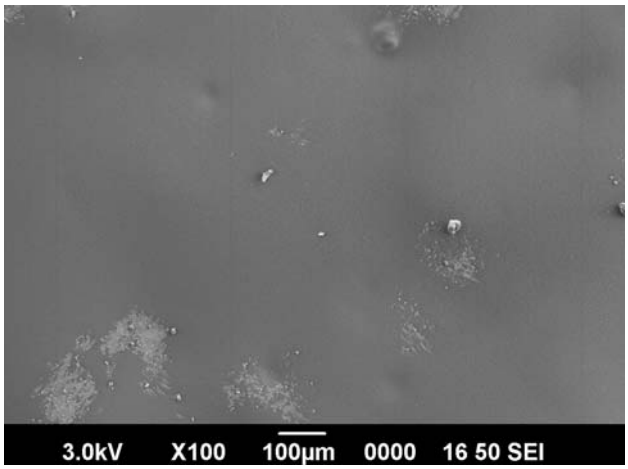

Fig. 4 SEM image of the polymeric membrane of D_{P8} sensor

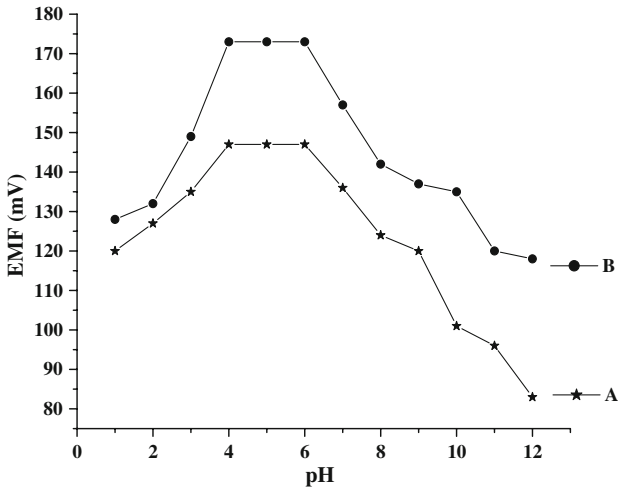

Fig. 5 Effect of pH on the cell potential of the DOM selective PVC membrane sensor D_{P8} at 1.0×10^{-4} M (**A**) and 1.0×10^{-3} M (**B**)

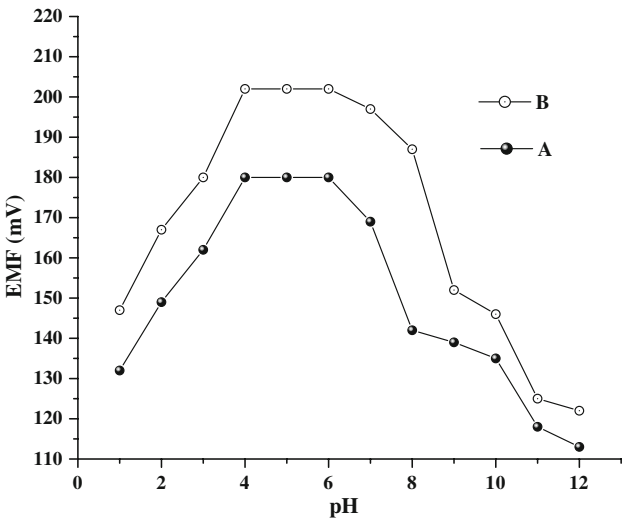

Fig. 6 Effect of pH on the cell potential of the DOM selective carbon paste sensor Dc_5 at 1.0×10^{-4} M (**A**) and 1.0×10^{-3} M (**B**)

response characteristics such as high sensitivity and long shelf life. The deviation of slope of the sensor D_{P8} from the Nernstian value may be due to its irregular or less uniform surface.

3.3 Effect of concentration of internal filling solution

The influence of the concentration of the internal filling solution on the potential response of the DOM selective membrane sensor was studied. The proposed membrane electrode was examined with different concentrations of the internal solution from 1.0×10^{-2} to 1.0×10^{-4} M of DOM. The variation in concentrations of DOM did not cause any effect on the functioning of the membrane sensor. For the carbon paste electrode, there is no need for an internal filling solution. This is one of the significant advantages of the carbon paste sensor.

3.4 Effect of pH

The effect of pH on the potential of the developed sensors was examined for two fixed concentrations (1.0×10^{-3} and 1.0×10^{-4} M). The pH range was varied between 1 and 12 using different buffer solutions. Figures 5 and 6 clearly depict that the potentials remained constant in the pH range 4–6 for both the electrodes. The potential decrease at pH less than 4 may be due to the gradual increase in the protonated species. At pH greater than 6, the solution turned turbid due to the decomposition of the drug, and potential values were observed to decrease. The

variations in concentration of DOM did not affect the useful pH range of the two sensors developed.

3.5 Selectivity studies

The preference of a sensor for a particular analyte in presence of other foreign species is determined from the selectivity coefficient values. The interference of various substances on the selectivity of the developed sensors has been examined using the fixed interference method [27]. The potentiometric selectivity coefficients were evaluated graphically using the expression $K^{pot}_{A,B} = a_A/(a_B)^{z_A/z_B}$ where a_A is the activity of the primary ion which is varied, a_B, is the activity of the interfering ion which is fixed, z_A and z_B are charge numbers of the primary ion, A and of the interfering ion, B. The resulting selectivity coefficients are summarized in Table 4. The values of selectivity coefficients given in the table reveal that the developed sensors show very good selectivity to DOM in the presence of ions such as NH_4^+, K^+, Na^+, Mg^{2+}, Co^{2+}, Ni^{2+}, Ca^{2+}, Zn^{2+}, lactose, urea, ascorbic acid, and glycine. There were no interferences from the tablet excipients such as starch and talc, and hence, the sensors can be selectively used for the determination of DOM in tablets.

3.6 Response time and life time of the sensors

The average response time is the time required for the sensor to reach a stable potential within ±1 mV of the final equilibrium value. Response time of the DOM–PTA membrane sensor was less than 25 s and that in the case of carbon paste sensor was less than 20 s. The life time of an electrode is limited by the diffusion of the membrane components from the membrane to the aqueous solution [28–30]. The life time of the electrodes were investigated by measuring the potentials in standard drug solutions each day. The response slope of the sensors was calculated each time. A Nernstian slope was obtained for a period of 3 weeks in the case of membrane sensor and 2 weeks for carbon paste sensor. During this period, the sensors showed no significant deviation in the optimized response characteristics.

The statistical calculations for the developed sensors were carried out using the calibration graphs for the pure drug. The results of the determination are incorporated in Table 5. From the table, it is clear that the sensor D_{P8} with a slope value of 56.5 mV/decade has a LOQ value of 1.54×10^{-5} M and RSD value of 1.48. The sensor D_{C5} on the other hand gave a slope value of 57.8 mV/decade and LOQ as 3.71×10^{-5} M. The RSD value for this sensor was obtained as 1.32.

3.7 Determination of DOM in pharmaceutical formulations (tablets)

The developed sensors D_{P8} and D_{C5} were applied for the determination of DOM in commercially available pharmaceutical formulations such as Vomihtop (Cipla, India) and Domitil (Bal Pharma, India). The results were compared with those obtained by the standard method (potentiometric titration) in European Pharmacopoeia [31]. The results are illustrated in Table 6. The data given in the table clearly indicate a satisfactory agreement between the DOM content determined by the proposed sensors and by the reported standard method.

3.8 Recovery of DOM from urine sample

The developed sensors were applied for the determination of the drug from urine samples. The results of the determination are summarized in Table 7. The results show that

Table 4 Selectivity coefficient values of various interfering species, K^{pot}

Interfering species	K^{pot}	
	PVC membrane sensor D_{P8}	Carbon paste sensor Dc_5
NH_4^+	3.8×10^{-4}	4.7×10^{-4}
K^+	3.4×10^{-3}	2.9×10^{-3}
Na^+	5.6×10^{-3}	7.4×10^{-3}
Mg^{2+}	7.8×10^{-2}	6.2×10^{-2}
Co^{2+}	5.7×10^{-2}	8.3×10^{-2}
Ca^{2+}	3.7×10^{-3}	4.1×10^{-3}
Ni^{2+}	6.1×10^{-3}	4.9×10^{-3}
Zn^{2+}	7.3×10^{-3}	8.7×10^{-3}
Urea	5.6×10^{-3}	6.7×10^{-3}
Ascorbic acid	3.4×10^{-2}	2.1×10^{-2}
Glycine	8.4×10^{-3}	9.4×10^{-3}
Talc	3.8×10^{-2}	4.2×10^{-2}
Starch	4.3×10^{-2}	3.9×10^{-2}
Lactose	4.3×10^{-3}	5.2×10^{-3}

Table 5 Results of the determination of domperidone (pure form) showing the statistical calculations

Sensor	Composition (mg)	Slope (mV/decade)	LOQ (M)	RSD
D_{P8}	1.2 (ion pair) 50.2 (PVC) 48.6 (plasticizer BEP)	56.5	1.54×10^{-5} M	1.48
D_{C5}	2.2 (ion pair) 40.2 (graphite) 57.6 (plasticizer DBP)	57.8	3.71×10^{-5} M	1.32

Table 6 Determination of DOM in pharmaceutical formulations (tablets)

Sample	Declared amt (mg/tablet)	Method adopted	Found[a] (mg/tablet)	SD	CV
Vomihtop (Cipla, India)	10	D_{P8}	8.71	0.29	3.33
		Dc_5	9.23	0.22	2.38
		Standard method	9.34	0.21	2.25
Domitil (Bal Pharma, India)	10	D_{P8}	9.14	0.28	3.06
		Dc_5	8.33	0.25	3.00
		Standard method	9.63	0.19	1.97

[a] Average of six replicates

Table 7 Determination of DOM in urine sample using the developed sensors

Drug taken (M)	Sensor	Drug found[a] (M)	Recovery (%)	RSD
3.00×10^{-3}	D_{P8}	2.97×10^{-3}	99.0	0.23
	Dc_5	2.98×10^{-3}	99.3	0.38

[a] Average of six replicates

the proposed sensors can detect the investigated drug in spiked urine samples with high accuracy and high % recovery without pretreatment procedures of the sample.

4 Conclusions

Two domperidone selective sensors, viz: a PVC membrane sensor as well as a carbon paste sensor, have been developed using the ionophore DOM–PTA. The developed sensors are found to have good characteristics in terms of slope, concentration range, detection limit, response time, and pH range. The carbon paste sensor was found to be superior to the PVC membrane sensor in terms of linear range, detection limit, and also fast response time. The sensors are cost effective, and easy to prepare and to use. The sensors are also found to be highly selective over a number of other ions. Further, the developed sensors can be used for the determination of DOM content in pharmaceutical formulations and also in urine samples with high accuracy and precision.

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