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Short communication

Iron(II)-phthalocyanine as a novel recognition sensor for selective potentiometric determination of diclofenac and warfarin drugs

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Abstract

Construction and characterization of potentiometric membrane sensors for quantification of diclofenac and warfarin drugs are described. The membranes of the sensors incorporate 1.8 wt.% iron(II)-phthalocyanine (Pc) as a molecular recognition reagent, 64.3 wt.% dibutylsebacate (DBS) solvent mediator, 1.8 wt.% tridodecylmethylammonium chloride (TDMAC) as membrane additive and 32.1 wt.% poly(vinyl chloride) (PVC) as a matrix. The sensors display linear response for 1×10^{-2} to 9×10^{-6} mol l^{-1} (detection limit 5.4×10^{-6} mol l^{-1}) and 1×10^{-2} to 5×10^{-6} mol l^{-1} (detection limit 3×10^{-6} mol l^{-1}) with anionic slopes of -61 ± 1 and -63 ± 1 mV decade^{-1} over the pH range 5.5–9 for declofenac and warfarin, respectively. Validation of the assay methods according to the quality assurance standards confirms their suitability for quality control purposes. Use of the sensor for the assay of various formulations of the drugs shows a mean average recovery of 99.7% of the nominal values and a mean precision of ±0.3%. Significantly improved accuracy, precision, response time, stability, selectivity and sensitivity are offered by these simple and cost-effective potentiometric sensors compared with other standard techniques.

Keywords: Iron(II)-phthalocyanine; Lipophilic additives; Potentiometry; Pharmaceutical analysis; Diclofenac; Warfarin; PVC membrane sensors

1. Introduction

Metal phthalocyanines, porphyrins and corrins have been recently advocated as recognition elements for some anions. Owing to their ligand discriminating ability, these compounds appear to be one of the most promising classes of ionophores used in anion membrane potentiometric sensors [1–5]. In these systems, anion selectivity is achieved by specific anion axial ligation reactions with the central metal ion of the complex at the organic membrane/aqueous sample interface by either neutral or charged carrier type response mechanism [6]. Consequently, the properties of the central metal of these ionophors play an important role in governing the selectivity pattern.

It has been reported that phthalocyanines form stable complexes with a variety of metals [7] and such complexes can coordinate anions at the axial coordination site of the complex, thereby opening a new route for designing anion selective ionophores. Ion-selective membrane sensors incorporated metal phthalocyanines and their derivatives have been used for determination of salicylate [8], nitrite [4,9], ascorbate [8,10], sulfide [11], iodide [12] and sulfate [13] ions.

On the other hand, methods available in the literature for the determination of diclofenac, which has been extensively used for the treatment of active rheumatoid arthritis, asteoarthrosis and warfarin, which is commonly utilized as anti-coagulant rodenticides, include high performance liquid chromatography [14–20], capillary electrophoresis [21–24], amperometry [25], spectrophotometry [26–29] and fluorimetry [30–33]. Most of these methods require sophisticated equipments, involve several manipulation steps and entail derivatization reactions. The United States (USP) and

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British (BP) Pharmacopoeias described non-selective non-aqueous titrimetric procedures for diclofenac and warfarin [34,35]. Potentiometric sensors for determining both drugs are very limited and those published are based on the use of ferroin–drug associate complexes [36–38]. Selectivity of sensors based on ion-association complexes is low and suffer from interferences by many common ions.

In this paper, we describe new potentiometric membrane sensors for quantification of both diclofenace and warfarin drugs based on the use of iron(II)-phthalocyanine as a molecular recognition system in plasticized PVC membranes. This compound significantly enhances the selectivity of the sensor towards the primary drug ions. The developed sensors display high selectivity, long term stability, fast response and applicability over a wide range of pH and drug concentrations. Assay methods with these sensors require no prior treatment of the drug formulations, are simple, rapid, accurate, selective, cost-effective and, thus, suitable for routine drug analysis and for quality control/quality assurance program in drug industry.

2. Experimental

2.1. Reagents

All chemical used were of analytical reagent grade unless otherwise stated and doubly distilled deionized water was used throughout. High molecular weight poly(vinyl chloride) powder (PVC), 2-nitrophenyloctylether (*o*-NPOE), dibutylsebacate (DBS) and Fe(II)-, Cu(II)-, Co(II)-, Cr(III)-, Ni(II)-4,4′,4″,4‴-tetraaminophthalocyanines were obtained from Aldrich Chemical Co. (Milwaukee, WI). Tridodecylammonium chloride (TDMAC) was obtained from Fluka (Ronkonkoma, NY). Tetrahydrofuran (THF) (freshly distilled prior to use) was obtained from BDH (Poole, England). Pure diclofenac and warfarin powders were obtained from El-Nasr Pharmaceuticals and Chemicals Co. (Egypt). Dosage forms containing warfarin and diclofenac were obtained from local drug stores.

2.2. Equipment

Electrochemical measurements were made at room temperature ($25 \pm 1\,^{\circ}C$) with a Cole–Parmer 5800–05 pH millivoltmeter using diclofenac and warfairn membrane sensors in conjunction with a double-junction Ag–AgCl reference electrode (Orion Model 90–02) containing 10% (w/v) potassium nitrate in the outer compartment. Orion Research Expandable ion Analyzer EA 920 with a combination glass electrode (Orion H11332) was used for all pH measurements.

2.3. Drug membrane sensors

A 10 mg portion of iron(II)-phthalocyanine was mixed with 10 mg TDMAC, 360 mg of dibutylsebacate and 180 mg of PVC. The mixture was dissolved in ~7 ml THF in a glass Petri dish (~5 cm diameter), covered with filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature. Disks (0.7 mm o.d.) were cut from the parent membrane, mounted in the electrode body (0.4 mm o.d.) and the sensors were prepared as previously described [39–41]. The inner filling solution was an equal volume of 10^{-2} mol l^{-1} of diclofenac or warfarin solution with 10^{-2} mol l^{-1} potassium chloride. The internal reference electrode was a 3 mm diameter Ag/AgCl wire. The sensors were conditioned before use by soaking in 10^{-2} mol l^{-1} drug solution (for at least 24 h) and stored in the same solution when not in use.

2.4. Calibration of the sensors

Calibration was made by immersing the diclofenac or warfarin membrane sensor in conjunction with a double junction Ag–AgCl reference electrode in 50 ml beakers containing 10 ml aliquots of standard 1.0×10^{-6} to 1.0×10^{-2} mol l^{-1} drug solution. The pH of the solutions was adjusted to 7.2 using phosphate buffer. The potential readings were recorded for the drugs starting from the low to the high concentrations, when became stable. The potential response was plotted as a function of the logarithm of the drug concentrations. The calibration plot was used for subsequent measurements of unknown drug concentrations.

2.5. Sensor selectivity

The potentiometric selectivity coefficients ($K^{pot}_{Drug,B}$) of the sensors were determined using the separate solutions method [42]. A 1.0 ml aliquot of 1.0×10^{-2} mol l^{-1} of the drug solution was transferred into a 50 ml beaker containing 9.0 ml of phosphate buffer of pH 7.2. The drug sensor in conjunction with a double junction Ag–AgCl reference electrode was immersed in the solution and the potential reading was measured (E_{Drug}). In a separate run, a 1.0 ml aliquot of 1.0×10^{-2} mol l^{-1} of the interfering solution was transferred into a 50 ml beaker containing 9.0 ml of the same buffer and the potential reading was recorded (E_B). Selectivity coefficients were calculated from the equation:

$$-\log K^{pot}_{Drug,B} = \frac{E_{Drug} - E_B}{S}$$

where E_{Drug} and E_B are the emf readings of 1.0×10^{-2} mol l^{-1} drug and interferent solutions, respectively, and S is the sensor calibration slope (mV decade^{-1}).

2.6. Determination of diclofenac and warfarin in pharmaceutical preparations

The contents of five tablets of diclofenac or 50 tablets of warfarin were finely powdered in a small dish. An accurately weighed portion of the powder equivalent to 50 mg diclofenac or 35 mg warfarin was dissolved in about 20 ml distilled deionized water and filtered into a 50 ml volumetric

flask. The solutions were completed to the mark with phosphate buffer of pH 7.2. An aliquot (10.0 ml) of each solution was transferred to a 50 ml beaker and the drug sensor in conjunction with a double junction reference electrode were immersed in the solution. The potentials of the sensors were measured and compared with the calibration graph. Alternatively, the potentials were measured before and after addition of 1.0 ml of 10^{-2} mol l^{-1} standard diclofenac or warfarin solution to the test solution and the unknown concentration was calculated using the standard addition method [41].

3. Results and discussion

Potentiometric poly(vinyl chloride) matrix membrane sensors incorporated iron(II)-, copper(II)-, cobalt(II)-, nickel(II)- and Chromium(III)-phthalocyanines as neutral carriers were prepared. The membranes were plasticized with either dibutylsebacate or *o*-nitrophenyloctylether and doped in diclofenac and warfarin drug solutions. The sensors were electrochemically evaluated for both drugs according to IUPAC recommendations [42]. Since Fe(II), Cu(II), Co(II), Ni(II) and Cr(III) atoms are all 3d elements having similar electronic structures, it was expected that sensors based on phthalocyanines containing these metals would exhibit similar potentiometric response characteristics. The results showed, however, that Ni(II)- and Cr(III)-phthalocyanines based membrane sensors gave very poor potentiometric response for diclofenac and warfarin, whereas Fe(II)-, Co(II)- and Cu(II)-phthalocyanines based membrane sensors displayed almost the same good performance characteristics for diclofenac. Fe(II)-phthalocyanine exhibits good response characteristics for warfarin. Sensor incorporated membranes plasticized with DBS showed better responses than those incorporated *o*-NPOE. Iron(II)-phthalocyanine at concentration levels < 2 wt.% readily dissolved in the membrane solvent to give a transparent homogenous membrane. All subsequent study was made with iron(II)-phthalocyanine recognition system and DBS solvent mediator.

It is apparent from these data that the nature of metal substituted phthalocynines affects the potentiometric response of the membranes sensors. The sensing mechanism can be explained on the bases of electrostatic interaction and coordination of the drug by axial ligation to phthalocyanine central metal ions (Fig. 1). The form in which iron(II)-phthalocyanine exist neither affect the coordination with the drug anions nor the potential response of the sensor because both the monomer and oxobridged dimers forms have axially coordination sites available for interaction with drug anions [43]. The coordination or interaction between metal-phthalocyanine carriers and drug anions can be treated by the concept of generalized acid–base reaction and the acidity of the central metal determines the coordination strength with the drug anion as well as the selectivity towards the primary drug anions with respect to other anions.

3.1. Influence of lipophilic ionic additives

Membrane sensors were constructed by incorporating lipophilic ionic sites within the membrane components. The exact nature of the sites required to enhance selectivity, depends on the operative mechanism of anion–carrier interaction in the membrane. Addition of ionic sites for neutral carrier based liquid polymeric membranes enhance the potentiometric selectivity. Furthermore, it was found that such ionic additives are beneficial in terms of reducing the sensors response time and lowering the membrane resistance [44]. It has also been suggested that examining the role of lipophilic ionic additives on the selectivity of polymeric membrane sensors can be used as a diagnostic tool to determine the operative response mechanisms [45]. Herein, the effect of addition of lipophilic cationic site (e.g., tridodecylmethylammonium chloride, TDMAC) to the membrane in ratios ranging from 0.5 to 1.5 mol% relative to iron(II)-phthalocyanine was examined by incorporation of TDMAC in the plasticized PVC Fe(II)-phthalocyanine–DBS. The optimum membrane composition was 1.8 wt.% Fe(II)-Pc, 32.1 wt.% PVC, 64.3 wt.% DBS and 1.8 wt.% TDMAC. After doping the membranes in diclofenac or warfarin solution, the sensor was electrochemically evaluated. The results in Table 2, show nearly 10-fold improvement of the sensor selectivities over most other anions are obtained due to the presence of TDMAC. However, in the presence of TDMAC, the lower linear response range and calibration slope slightly declined.

3.2. Performance characteristics of the sensors

Sensors incorporating iron(II)-phthalocyanines PVC membranes plasticized with (DBS) were prepared with the composition 1.8 wt.% metal phthalocyanine, 32.1 wt.% PVC, 1.8 wt.% TDMAC and 64.3 wt.% DBS. The sensors show linear potentiometric response over the concentration ranges of 9×10^{-6} to 1.0×10^{-2} and 1.0×10^{-2} to 5.0×10^{-6} mol l^{-1}

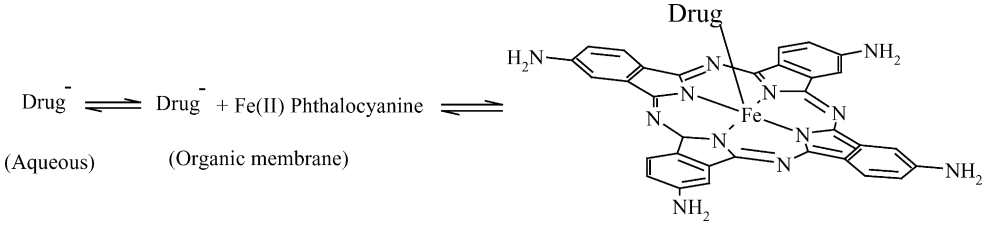

Fig. 1. Mechanism of the response of iron(II) 4,4′,4″,4‴-tetraamino-phthalocyanine in the membrane phase to the drug anions.

Table 1
Potentiometric response characteristics of Fe(II)-Pc–DBS membrane sensors for diclofenac and warfarin in the absence and presence of TDMAC as membrane additive

Parameter	Diclofenac		Warfarin	
	Fe(II)-Pc–DBS	Fe(II)-Pc–TDMAC–DBS	Fe(II)-Pc–DBS	Fe(II)-Pc–TDMAC–DBS
Slope (mV decade^{-1})	-55 ± 1	-61 ± 1	-59 ± 1	-63 ± 1
Intercept (mV)	10 ± 1	-28 ± 1	-47 ± 1	-36 ± 1
Correlation coefficient (r)	0.998	0.998	0.998	0.998
Lower limit of linear range (mol l^{-1})	6.0 ± 10^{-6}	9.0 ± 10^{-6}	3.0 ± 10^{-6}	5.0 ± 10^{-6}
Lower limit of detection (mol l^{-1})	4.4 ± 10^{-6}	5.4 ± 10^{-6}	2.1 ± 10^{-6}	3.0 ± 10^{-6}
Working range (pH)	5.7—9.0	5.5–9.0	5.8–7.3	6.0–8.0
Response time for 1×10^{-2} mol l^{-1} (s)	<5	<10	<15	<10
Life span (week)	14	16	13	15
Accuracy (%)	98.1	98.8	98.7	98.9
Repeatability, CV_w (%)	0.8	1.1	0.9	1.2
Between day-variability, CV_b (%)	1.2	1.3	1.1	1.3
Standard deviation, σ (%)	1.2	1.4	1.3	1.3

with anionic slopes of -66 ± 1, and -63 ± 1 mV decade^{-1} for diclofenac and warfarin, respectively (Table 1). The response times of the sensors were less than 15–30 s for 10^{-6} to 10^{-2} mol l^{-1} diclofenac and warfarin drugs. The life span of the sensors was about 15 weeks.

3.3. Effect of pH

The influence of the pH on the potential response of diclofenac and warfarin based membrane sensors was tested using 10^{-4}, 10^{-3} and 10^{-2} mol l^{-1} drug solutions over the pH range 2–10. Adjustment of pH was carried out using KOH and/or H_3PO_4. From pH-potential profiles, it is apparent that there is no change in potential response within the pH range 5–8. The sensors display, however, a significant response at high pH values (> pH 8) probably originating from the ability of hydroxide ions to compete favourably for axial coordination site of the central metal. At pH < 5, there was also an interference due to the increase of hydrogen ions concentration and precipitation of the free acidic drugs.

3.4. Effect of interfering ions

The potentiometric selectivity coefficients ($K^{pot}_{Drug,B}$) of diclofenac and warfarin sensors based on iron(II)-phthalocyanines (DBS plasticizer) with and without TDMAC were determined using the separate solutions (SSM) method [42] at a concentration level of 10^{-2} mol l^{-1} of both drug solution and interfering anions. Influences of 18 different organic and inorganic anions on the response of the sensors were evaluated by measuring the selectivity coefficients. The results are listed in Table 2. The results obtained show that these sensors display significantly high selectivity for diclofenac and warfarin over many common organic and in-

Table 2
Potentiometric selectivity coefficients ($K^{pot}_{Diclo,B}$) of Fe(II)-Pc–DBS membrane sensors for diclofenac and warfarin in the absence and presence of TDMAC as membrane additive

Interfering ion, B	$K^{pot}_{Diclo,B}$		$K^{pot}_{Warf,B}$	
	Fe(II)-Pc–DBS	Fe(II)-Pc–TDMAC–DBS	Fe(II)-Pc–DBS	Fe(II)-Pc–TDMAC–DBS
Cl^-	3.3×10^{-3}	5.3×10^{-3}	2.9×10^{-3}	1.0×10^{-3}
Br^-	3.5×10^{-3}	4.7×10^{-4}	2.9×10^{-3}	7.6×10^{-4}
I^-	7.1×10^{-3}	1.4×10^{-3}	4.7×10^{-3}	3.9×10^{-3}
IO_3^-	3.0×10^{-3}	5.5×10^{-4}	4.3×10^{-3}	6.8×10^{-4}
NO_2^-	3.3×10^{-3}	6.8×10^{-4}	2.7×10^{-3}	5.3×10^{-4}
NO_3^-	3.0×10^{-3}	9.6×10^{-3}	3.0×10^{-3}	1.9×10^{-3}
SO_4^{2-}	3.0×10^{-4}	7.1×10^{-4}	3.3×10^{-3}	3.9×10^{-4}
CNS^-	7.5×10^{-3}	3.1×10^{-4}	6.0×10^{-3}	1.2×10^{-3}
PO_4^{3-}	7.7×10^{-4}	1.5×10^{-4}	8.8×10^{-3}	2.0×10^{-3}
Oxalate	3.0×10^{-3}	1.5×10^{-4}	1.1×10^{-3}	1.2×10^{-4}
Tartrate	6.5×10^{-4}	2.5×10^{-4}	1.5×10^{-3}	1.8×10^{-4}
Citrate	2.8×10^{-4}	1.6×10^{-4}	1.0×10^{-3}	1.2×10^{-4}
Benzoate	1.4×10^{-3}	5.5×10^{-4}	3.3×10^{-3}	3.3×10^{-4}
Formate	6.0×10^{-3}	7.7×10^{-4}	4.9×10^{-3}	8.2×10^{-4}
Salicylate	1.8×10^{-4}	2.0×10^{-3}	3.8×10^{-3}	4.0×10^{-3}
Phthalate	6.5×10^{-4}	5.5×10^{-4}	2.6×10^{-3}	1.2×10^{-3}
Maltose	2.0×10^{-4}	7.1×10^{-5}	2.1×10^{-4}	4.8×10^{-5}
Glucose	3.9×10^{-3}	6.1×10^{-4}	3.5×10^{-3}	6.0×10^{-4}

organic anions. Sensors incorporating TDMAC in the membranes exhibit better selectivity compared with those without TDMAC. The effect of drug excepients and diluents (e.g., carboxymethyl cellulose, glucose, lactose, maltose, magnesium stearate, mannitol, starch and talc powder) was also examined. Up to 10^4-fold excess of these substances has no effect on the response of the sensors. The selectivity coefficients obtained by these sensors are better by a factor of 10–100 over those based on the use of other ionophores [36–38].

3.5. Determination of diclofenac and warfarin in pharmaceutical preparations

The validity of the proposed potentiometric methods for determining diclofenac and warfarin was assessed by measuring the range, lower limit of detection (LOD), accuracy (recovery), precision or repeatability (CV_w), between-day-variability (CV_b), linearity (correlation coefficient) and sensitivity (slope) [46]. Data obtained on six batches (six determinations each) with standard 0.01–3 mg ml^{-1} diclofenac sodium and 0.33–3.3 mg ml^{-1} warfarin solutions using the calibration graph method show results with average recoveries of 99.7 and 99.8% and mean standard deviations of ±0.3 and ±0.2% for diclofenac and warfarin, respectively.

Diclofenac and warfarin were also determined in various dosage forms. The results obtained for diclofenac with Fe(II)-Pc–DBS, based membrane sensor showed an average recovery of 99.4%, and a mean standard deviation of ±0.2%,

Table 3
Determination of diclofenac in some pharmaceutical preparations using Fe(II)-Pc–DBS, TDMAC-PVC membrane sensor

Trade name and source	Nominal content[b] (mg tablet^{-1})	Recovery[a] (%)
Declophen (Pharco Pharm., Egypt)	25	99.8 ± 0.3
Voltaren (Swiss Pharm., Egypt)	25	100.0 ± 0.2
Voltaren (Swiss Pharm., Egypt)	50	99.5 ± 0.2
Voltaren (Swiss Pharm., Egypt)	100	100.0 ± 0.1
Cataflam (Swiss Pharm., Egypt)	25	98.7 ± 0.3
Diclophenac (El-Nasr Pharm. Chem. Co., Egypt)	25	98.7 ± 0.2
Diclophenac (El-Nasr Pharm. Chem. Co., Egypt)	50	98.9 ± 0.4

[a] Average of six measurements.
[b] The active ingredient of all drugs is diclofenac sodium except for cataflam, for which the active ingredient is diclofenac potassium.

Table 4
Determination of warfarin in some pharmaceutical preparations using Fe(II)-Pc–DBS, TDMAC-PVC membrane sensor

Trade name and source	Nominal content (mg tablet^{-1})	Recovery[a] (%)
Hemofarin (ADWIC Pharm., Egypt)	1	99.1 ± 0.2
	2	99.1 ± 0.1
	3	96.4 ± 0.4
	5	99.3 ± 0.4

[a] Average of six measurements.

Table 5
Comparison of some instrumental methods used for the determination of diclofenac and warfarin

Method	Working range (μg ml^{-1})	Recovery (%)	Pretreatment step	Reference
Diclofenac				
HPLC	7–35	101.1	None	[17]
	0.05–10	90.2	Separation	[18]
Capillary electrophoresis	5–45	NR	None	[21]
Spectrophotometry	5–40	NR	Extraction	[26]
	0.8–6.4	NR	Extraction	[27]
	3–14.8	95.6	None	[28]
	5–50	98.3–100.6	None	[29]
Fluorimetry	0.29–0.03	NR	None	[30]
	0.2–5.0	98.6	None	[31]
Potentiometry	1.1–3180	99	None	[36]
	7.3–3180	98	None	[37]
	1.0–3180	99.7	None	Present work
Warfarin				
HPLC	0.013–2.5	83.5	Extraction	[19]
	0.001–0.1	92.5	Extraction	[20]
Capillary electrophoresis	0.02–2	NR	Derivatization	[24]
Fluorimetry	0.7–2.1	102	None	[32]
	0.4–1.2	99–110	None	[33]
Amperometry	1–40	NR	None	[26]
Potentiometry	5.6–3300	97.2–102.9	None	[38]
	1.7–3300	99.7	None	Present work

NR: not reported.

(Table 3). Fe(II)-Pc–DBS–warfarin based membrane sensor showed an average recovery of 98.5% with a mean standard deviation of ±0.3% (Table 4). The results obtained for determining warfarin using the United States Pharmacopoeia and diclofenac by the standard assay method of meclofenamate sodium, which is structurally similar to diclofenac show a good correlation with those obtained by iron(II)-phthalocyanine based membrane sensor. An *F*-test revealed that there was no significant difference between the means and variances of the two sets of results.

Application of the proposed sensors for quality control/quality assurance of the homogeneity of the drugs tablets was also judged through calculation of the Student's *t*-value at 95% confidence limit and the results showed that the calculated *t*-value did not exceed the theoretical value, confirming the accuracy of the obtained results. Control charts (*R* and $\bar{X}$) prepared for monitoring the drugs over 1 month indicated that the assay under investigation using the proposed sensors was under statistical control [46].

A comparison of the performance of the proposed potentiometric sensors with other instrumental methods used for diclofenac and warfarin assessment (Table 5) reveals the advantages of simple fabrication, low cost and application over at least three decades of concentration without prior separation, extraction and derivatization steps commonly used with these techniques [18,26,27,19,20]. Furthermore, the lower limit of quantitation of the sensors are similar to these offered by some HPLC [17], capillary electrophoresis [26] and spectrophotometry [26,28,29]. On the other hand, the proposed sensors possess four distinct advantages over the previous potentiometric systems [36–38]. These are the longer life span (≥15 weeks), lower selectivity coefficients for most interferents (10^{-3} to 10^{-5}), shorter response time (≤10 s) and better detection limits (1–1.7 μg ml^{-1}).

4. Conclusions

Simple and direct potentiometric assay methods for determining declofenac and warfarin are described based on the use of Fe(II)-phthalocyanine as molecular recognition system in plasticized poly(vinyl chloride) membranes containing TDMAC as anionic additive. This approach is cost-effective and offers the advantages of high accuracy, sensitivity, fast response and utilization for direct quantification of diclofenac and warfarin in dosage forms at room temperature without prior treatments. This warrant application of the technique for quality control/quality assurance in the drug production.

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