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An electrode immobilized in a graphite matrix with ion pair complex for the determination of diclofenac in pharmaceuticals

Zholt Kormosh [a,*], Iryna Hunka [a], Yaroslav Bazel [b]

[a] *Volyn National University, Lutsk, Ukraine*
[b] *P.J. Safaric University, Slovakia*

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Abstract

A simple, precise, rapid and low-cost potentiometric method for diclofenac determination in pharmaceuticals is proposed. A new diclofenac-sensitive electrode was constructed by incorporating the diclofenac ion pair complex with butyl rhodamine B into graphite matrix. The electrode exhibited a linear response over the concentration range of $1 \times 10^{-4} - 5 \times 10^{-2}$ mol L^{-1}, a detection limit of 3.9×10^{-5} mol L^{-1} with a Nernstian slope of 61 ± 2 mV $decade^{-1}$. The working pH range is 6-11. The electrode is easily constructed, has fast response time (3-11 s) and can be used for the period of six months without any considerable deterioration. The proposed sensor displays good sensitivity for diclofenac in the presence of several substances. It was used to assay diclofenac in pharmaceuticals.

Keywords: Diclofenac, Potentiometry sensors, Pharmaceutical analysis

1. Introduction

Ion-selective electrodes (ISEs) belong to the oldest established chemical sensors and are comparatively well understood [1-4]. ISEs are able to transduce a chemical signal (concentration of an analyte in a sample) into a potentiometric signal: electromotive force of a cell including an ISE and a suitable reference electrode. Because of these advantages, ISEs became widely used in various applications: in clinical chemistry (blood, serum, urine, and saliva, in environ mental protection, agricultural, and foodstuff samples (natural and waste water, soil, vegetables, fruits, wines, milk, meat), and analytical chemistry in general [5].

The present work describes the development and application of a diclofenac selective electrode based on the diclofenac ion pair complex (Fig. 1) with butyl rhodamine B in a graphite matrix.

Diclofenac (DCF) as the sodium salt, is a benzeneacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino]benzene-acetic acid monosodium salt. It is used in the treatment of many diseases, such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, nonartricular rheumatism. It is formulated in pharmaceuticals as tablets, injections and ointments [6]. Analytical methods like fluorimetry [7-10], HPLC [11], gravimety [12], spectrophotometry [13-15] and partial least squares regression (PLS) [16-19] analysis have been developed to determine the diclofenac connect in pharmaceutical forms and biological fluids.

* Corresponding author. Tel.: +38 0332248427; fax: +38 0332241007
E-mail address: kormosh@univer.lutsk.ua (Zh. Kormosh)

Some of these methods are sophisticated instruments and for this reason they are not suitable for routine analysis. Methods for potentiometric diclofenac determination have been also described [20-26].

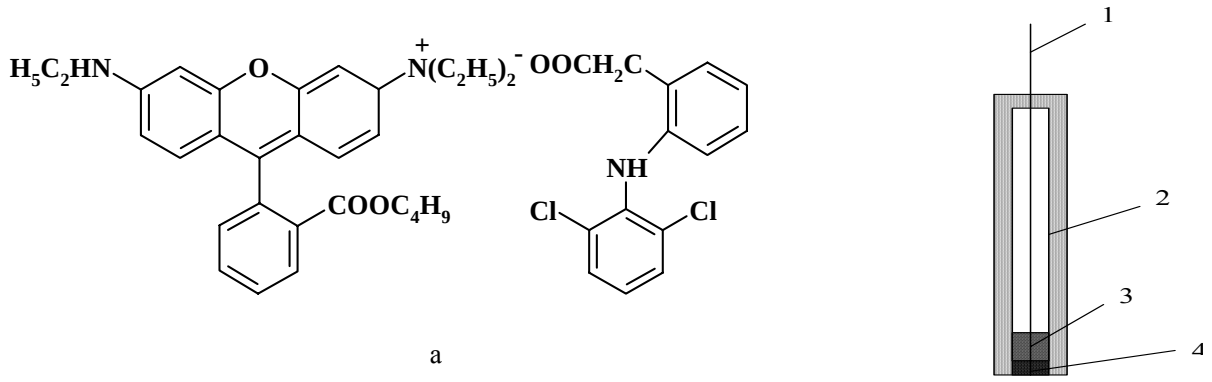

Fig. 1 (a) Ion associate of diclofenac with butyl rhodamine B and (b) Diclofenac electrode: 1- Cu wire (conductor cable), 2- PVC tube, 3- Alloy of Vud, 4-Sensor pellet (graphite |IA| TCP)

2. Experimental

2.1. Equipment

An I-160 M model pH/mV meter with Ag-AgCl reference electrode was used for the measurements of potential difference at 25.0 ± 0.1 ^{o}C.

2.2. Reagents

All chemicals were of analytical-reagent grade. Distilled water was used to prepare all solution and in all experiments. Dibutylphtalate (DBP), dibutylsebacate (DBS), dioctylphtalate (DOF), dinonilphtalate (DNF), tricresylphosphate (TCP) were obtained from Sigma-Aldrich. The 0.04 mol L^{-1} buffer solutions of pH 6-11 ranges were freshly prepared.

The freshly prepared aqueous standard solutions (1×10^{-7}-5×10^{-2} mol L^{-1}) of diclofenac (Sigma-Aldrich) were prepared in 0.04 mol L^{-1} of buffer solution (for the study of effect of pH) for analytical purposes. Buffer solutions (pH 6-11*)* were prepared by mixing corresponding amounts of 0.04 mol L^{-1} H_3BO_3, 0.04 mol L^{-1} CH_3COOH, 0.04 mol L^{-1} H_3PO_4 and 0.2 mol L^{-1} NaOH. The ionic strength was adjusted with 0.1 mol L^{-1} KCl.

The following commercial dosage forms were analyzed with new ion-selective electrode: Naclofen ointment (Slovenia) labeled to contain 1% of diclofenac diethylamine, Naclofen ampoules (Slovenia) 75 mg/3 mL of diclofenac (sodium salt), Dicloran® CP tablets (India) 100 mg of diclofenac (sodium salt) per tablet**.** Urine samples were obtained as follows. Before breakfast 5 healthy volunteers received a tablet of 1×100 mg Dicloran® CP; India. Urine samples were collected in the individual flasks after 5 hours of drug administration and analyzed.

2.3. Construction of the ion-selective electrode

An ion pair complex of diclofenac with butyl rhodamine B was prepared by mixing equal quantities of 1×10^{-2} mol L^{-1} DCF and 1×10^{-2} mol $L^{-1}$of butyl rhodamine B. The solution was settled during 2 hours and the sediment of ion pair complex was filtered (quantitative rapid filter paper). This residue was treated with 50 ml of cold distilled water. The filter paper containing the precipitate was dried for 24 h at room temperature. This ion pair complex was used as an

electrode-active substance in the preparation of the ion-selective electrode for diclofenac determination.

The ion-selective electrode was prepared as follows: a PVC tube (5.0 mm × 7.0 cm) was cleaned and degreased. A working end was a Wood alloy substrate (2.0 mm thick) to which the lead was soldered that formed a site for the deposition of the active component. Electrode active substance (an ion pair complex of diclofenac with base coloring agent butyl rhodamine B 0.02 g), DBP (0.02 ml) and pure powdered graphite (0.04 g) were mixed a mortar until a homogeneous paste was obtained. The paste was then deposited onto the prepared site and dried for 2 h. When not in use, the electrode was kept immersed in a small volume of 0.01 mol/L sodium diclofenac solution.

2.4. Sample preparation

Solid: Tablets were weighed and finely powdered. An accurately weighed portion equivalent to one tablet was dissolved in distilled water; filtered and transferred to a 50 mL volumetric flask with KCl (the ionic strength was maintained with 0.1 mol $L^{-1}$of KCl).
Ointment: An accurately weighed portion (10 g) of ointment was dissolved in distilled water, filtered and transferred to a 50 mL volumetric flask (the ionic strength was maintained with 0.1 mol L^{-1} of KCl). Samples of ointment were analyzed by the proposed ion-selective electrode using a calibration graph. This procedure was repeated 5 times.

Ampoule: A portion of 3 mL of ampoules (75 mg of diclofenac sodium) was transferred to a 50 mL volumetric flask with distilled water (the ionic strength was maintained with 0.1 mol L^{-1} of KCl). Samples were analyzed by the proposed ion-selective electrode using a calibration graph. This procedure was repeated 5 times.

3. Results and discussion

3.1. Electrode response

It is a well-known fact that sensitivity and selectivity of ion-selective electrodes depend significantly not only on the nature of an electrode active substance used but also on the content of the electrode active substance in the composition and the properties of the solvent mediators employed. A study of the effect of solvent mediators on the potentiometric response characteristics of the diclofenac ion-selective electrode based on the diclofenac ion pair complex with butyl rhodamine B were investigated and the results are summarized in Table 1. The corresponding emf responses are shown in Fig. 2. Significant difference in the potential response of the electrodes was found among the five different solvent mediators that were used.

Table 1
Characteristics of different electrode active substances with different solvent mediators of diclofenac ion-selective electrodes

Plasticize	Slope / mV	Linear range / mol L^{-1}	Detection limit / mol L^{-1}	Response time / s
DBP	62	1×10^{-4}-5×10^{-2}	3.9×10^{-5}	3-5
DBS	51	1×10^{-4}-5×10^{-2}	4.5×10^{-5}	5-10
TCP	58	1×10^{-4}-5×10^{-2}	4.0×10^{-5}	3-8
DOF	51	1×10^{-4}-5×10^{-2}	4.2×10^{-5}	3-7
DNF	57	1×10^{-3}-5×10^{-2}	1.4×10^{-4}	4-10

Note: Average of five determinations

The diclofenac ion-selective electrode made using DBP exhibited a calibration plot of a very good Nernstian slope for diclofenac concentrations between 1×10^{-4} and 5×10^{-2} mol L^{-1} with detection limit of 3.9×10^{-5} mol L^{-1} and E = –149.0 + 61.0 log [DCF].

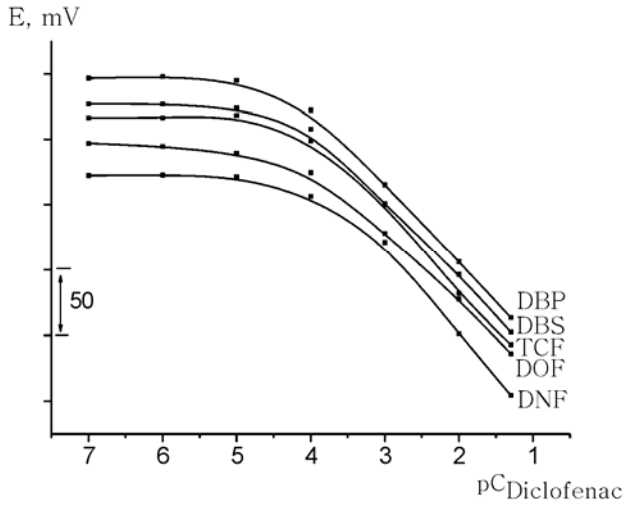

Fig. 2 Effect of the nature of the plasticizers on the response of the proposed electrode

Consequently, the electrode made using DBP was selected for carrying out the remaining studies. For analytical applications, the response time of a sensor is an important factor. The static response time of the electrode, tested by measuring the average required to achieve a potential within ± 1 mV of the final steady-state potential upon successive immersion of a series of diclofenac solutions, each having a tenfold difference in concentration, was within 10 s for diclofenac concentrations < 10^{-3} mol L^{-1}. The potential stayed constant for about 5 min, after which a very low divergence within the resolution of the millivoltmeter was observed. Its stability was checked over a period of 6 months.

3.2. Effect of pH

The most important factor of the functioning of the most all ion-selective electrodes is the medium acidity expressed as pH value. The reason for this is chemical processes involving the membrane components, the determined substance, and H_3O^+ or OH^- ions. Wide application of an ISE requires the knowledge of the pH range of the functioning of given electrode. This is especially important for the electrodes sensitive to organic anions. The medium acidity affects the state of an ion associate and other membrane components. A number of parallel protolytical processes take place at the membrane-solution interface that can be quite complicated. We have investigated the effect of pH on main electrode characteristics of our ISE based on the ion associate with a basic dye. Generally, the working pH range of an ISE with an ion associate is determined by the protolytic properties of the ion associate components [26].

The influence of pH on the potential response of diclofenac ion selective electrodes was tested using 1×10^{-7}-5×10^{-2} mol L^{-1} diclofenac solutions over the pH range of 6-11. Adjustment of pH was carried out using universal buffer solutions. It is apparent from pH-potential profiles that there is no change in potential response. So this entire range of pH can be taken as the working pH range of the electrode. It is one of the main and very important advantages of this diclofenac ion-selective electrode.

3.3. Effect of content of electrode active substance

The influence of the content of electrode active-substance electrodes on the potential response of different ion-selective was tested in the 11-60% range (adjusted with 0.1 mol L^{-1}

KCl). The results are shown in Table 2. Thus, the content of electrode active substance does not significantly modify the potential response.

Table 2
Characteristics of different ion-selective electrodes with different containing of electrode active substance

Containing of electrode active substance / %	Slope / mV	Linear range / mol L^{-1}	Detection limit / mol L^{-1}	Response time / s
11	64	1×10^{-4}-5×10^{-2}	8.9×10^{-5}	3-5
25	63	1×10^{-4}-5×10^{-2}	3.9×10^{-5}	3-5
36	60	1×10^{-4}-5×10^{-2}	1.6×10^{-4}	3-5
60	62	1×10^{-4}-5×10^{-2}	6.3×10^{-5}	3-5

Note: Average of five determinations

3.4. Potentiometric selectivity coefficients

An important characteristic of any ion-selective sensor is its response to the primary ion in the presence of other ions present in solution, which is expressed in terms of the potentiometric selectivity coefficient. The potentiometric selectivity coefficients for the diclofenac electrode were determined for a number of anions and some of cations by the matched potential method [2, 5, 27]. In this method the selectivity coefficient is defined by the ratio of the activity of the primary ion relative to an interfering ion when they generate identical potentials in the same reference solution. In this method both monovalent ions are treated in the same manner and the valence of the ions does not influence the selectivity coefficient.

The selectivity coefficients were calculated from the concentration of the interfering ion which induced the same amount of the potential change as that induced by the increase of the concentration of primary ion. An influence of 13 different organic and inorganic anions and of 4 cations on the response of the sensor was evaluated by measuring the selectivity coefficients. The resulting values of $-\log K_{DCF,I}$ are presented in Fig. 3. Obtained results show that these sensors display significantly high selectivity for diclofenac over many common organic and inorganic substances.

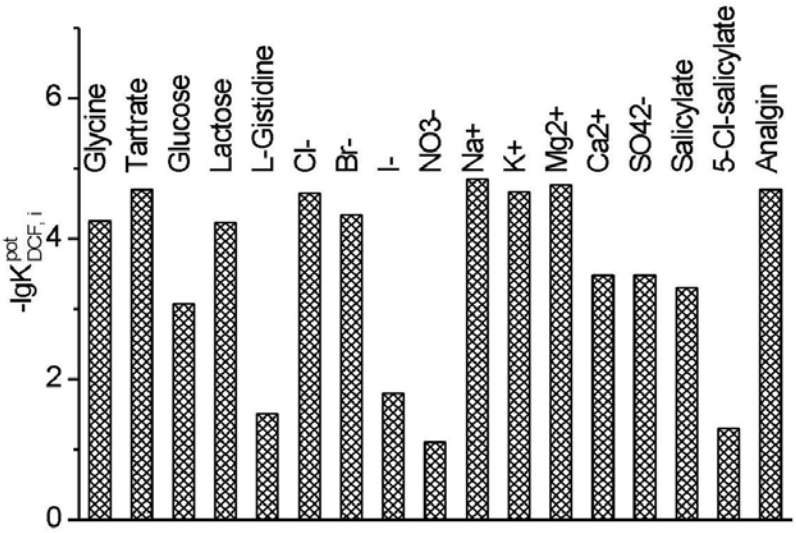

Fig. 3 Potentiometric selectivity coefficients of the diclofenac ion-selective electrode

No interference was noted for most of the compounds found along diclofenac in pharmaceutical formulations such as glycine, tartrate, glucose, lactose, L-histidine and others. In Table 3, the selectivity coefficients of the proposed paste electrode for some interfering ions are compared with the corresponding values previously reported for diclofenac ion selective electrodes [20-23]. A comparison of the proposed electrode with reported electrodes presented in Table 3 and in Table 4 indicates that the selectivity coefficients of the proposed electrode are similar or somewhat better than those reported for diclofenac ion selective electrodes.

Table 3
Comparison of the analytical performance of the proposed electrode with the reported diclofenac ion selective electrodes

Membrane	pH	Slope mV/pC	Linear range / mol L^{-1}	Detection limit / mol L^{-1}	Resp. time / s	Life time / weeks
Iron(II)-Phtalocyanine, [18]	7.2	-61.0 ± 1.0	9×10^{-6}-1×10^{-2}	5.4×10^{-6}	<10	16
		-55.0 ± 1.0	6×10^{-6}-1×10^{-2}	4.4×10^{-6}	<5	
Complex diclofenac with HDPB, [16]	6-9	-59.0 ± 1.0	1×10^{-5}-6×10^{-2}	4.0×10^{-6}	<10	>3
Pt|$Hg_2(DFC)_2$|graphite, [17]	7	-58.1 ± 0.8	5×10^{-5}-1×10^{-2}	3.2×10^{-5}	10-30	20
Ion associate diclofenac with butyl rhodamine B, *(this work)*	6-11	-61.0 ± 2.0	1×10^{-4}-5×10^{-2}	3.9×10^{-5}	5-10	18

3.5. Applications

Table 5 shows the results of proposed method that was successfully applied for diclofenac determination in pharmaceuticals (injectable ampoules, ointments and tablets). The diclofenac content of these solutions was then determined by the proposed electrode using the calibration method. The proposed electrode exhibits long lifetime, good stability, sensitivity, precision, and selectivity. It had rather good metrological characteristics, high sensitivity; it is low-cost, easy to prepare and to use. An electrode was developed by us is superior (especially in wide pH range of diclofenac determination and lifetime) compared to diclofenac ion-selective electrodes described in other methodologies of its potentiometric determination.

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Table 4
Comparison of the selectivity coefficients of the proposed electrode with the reported diclofenac ion selective electrodes

	Ion	Iron(II)-Phtalocyanine, [22]	Complex diclofenac with HDPB, [20]	|$Hg_2(DFC)_2$|Pt graphite, [21]	Present work
$-\lg K^{pot}_{DCF,I^-}$	Cl^-	2.3	2.6	0.36	4.7
	Br^-	3.3	3.3	–	4.3
	J^-	2.9	–	–	1.8
	JO_3^-	3.3	–	–	–
	NO_2^-	3.2	–	–	–
	NO_3^-	2.0	2.3	*	1.1
	SO_4^{2-}	3.0	–	3.9	3.9
	SCN^-	3.5	–	–	–
	PO_4^{3-}	3.8	–	–	–
	oxalate	3.8	–	2.1	–
	tartrate	3.6	–	–	4.7
	citrate	3.8	-	–	–
	benzoate	3.3	–	2.1	–
	salicilate	2.7	–	2.0	3.3
	5-Cl-salicilate	–	–	–	3.3
	phthalate	3.3	–	2.1	–
	glucose	3.2	2.8	*	3.1
	Mg^{2+}	–	3.2	–	4.8
	Ca^{2+}	–	3.1	–	3.5
	Na^+	–	1.3	–	4.9
	K^+	–	3.0	–	4.7
	glycine	–	2.6	–	4.3
	histidine	–	–	–	1.5
	benzyl alcohol	–	3.9	*	–
	perchlorate	–	–	*	–
	formate	–	–	3.7	–
	acetate	–	–	2.9	–
	lactose	–	–	–	4.2
	analgin	–	–	–	4.7

* No interference

Table 5
Potentiometric determination of diclofenac in some pharmaceutical formulations

Sample	Label amount, mg	Found [a]		Found by potentiometric titration [6]	
		mg	RSD	mg	RSD
Dicloran® CP tablet (India)	100	98.8 ± 1.6	1.3	99.9 ± 1.1	1.1
Naclofen injectable ampoule (Slovenia)	75	74.8 ± 1.1	1.2	75.0 ± 1.0	0.9
Naclofen-ointment (Slovenia)	100	101.2 ± 1.5	1.3	101.0 ± 1.1	1.1

[a] *n=5*, Confidence level of 95%. *Note:* RSD = relative standard deviation

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