Методы и объекты химического анализа, 2008, т. 3, № 1, С. 103–108.

Ion Selective Electrode Based on Ion Associate with Basic Dye for the Potentiometric Determination of Diclofenac

Zh. O. Kormosh[1], I. P. Hunka[1], R. V. Krakovyak[1], Ya. R. Bazel[2,3]

[1]*Volyn National University, Voli av., 13, 43025 Lutsk, Ukraine*
[2]*Uzhgorod National University, Pidgirna str., 46, Uzhgorod, Ukraine*
[3]*P.J. Safarik University, Moyzesova str., 11, 04154 Kosice, Slovakia*

Received: 10 October 2007 / Accepted: 15 January 2008

A simple, precise, rapid and low-cost potentiometric method for diclofenac determination in urine samples and pharmaceuticals is proposed. A new diclofenac-sensitive electrode was constructed by incorporating the diclofenac ion pair complex with rhodamine 6G into graphite matrix. The electrode exhibited a linear response over the concentration range of $1 \cdot 10^{-4}$–$5 \cdot 10^{-2}$ mol L^{-1}, a detection limit of $3.2 \cdot 10^{-5}$ mol L^{-1} with a Nernstian slope of 59 ± 2 mV $decade^{-1}$. The working pH range is 6–11. The electrode is easily constructed, has fast response time (3–10 s) and can be used for the period of five months without any considerable deterioration. The proposed sensor displays good sensitivity for diclofenac in the presence of several substances.

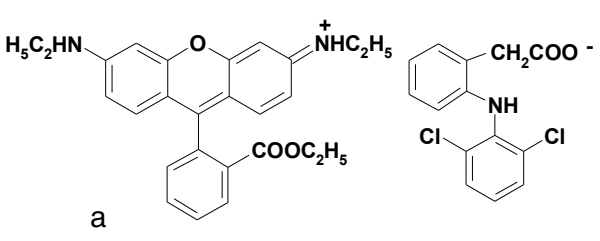
Keywords: *diclofenac · potentiometric sensors · pharmaceutical analysis*

Ion-selective electrodes (ISEs) belong to the oldest established chemical sensors and are comparatively well understand [1–4]. ISEs are able for transduction of 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 invar mental protection, agricultural, and foodstuff samples (natural and waste water, soil, vegetables, fruits, wines, milk, meat), and in process analytical chemistry [5].

The present work describes the development and application of a diclofenac selective electrode based on the diclofenac ion pair complex with rhodamine 6G (Fig. 1a) in graphite matrix. The advantages of this method are a fast and linear response over wide concentration and pH range, a good detection limit with high accuracy and reproducibility.

Diclofenac (DCF) is a benzeneacetic acid derivative, designated chemically as 2-[2-(2,6-dichlorophenyl)aminophenyl]ethanoic acid (often use 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 spectrophotometry [7–9], fluorimetry [10–12], HPLC [13], gravimety [14], UV spectrophotometry and partial least squares regression (PLS) [15–18] analysis have been developed to determine the diclofenac connect in pharmaceutical forms and biological fluids. 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 [19–24].

Recently, potentiometric sensors have become important and viable devices for use in chemical and pharmaceutical analysis.



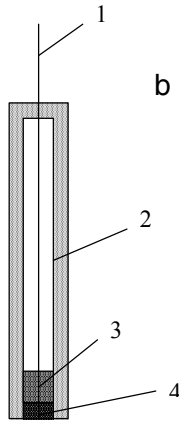


Fig. 1. Diclofenac ion pair complex with rhodamine 6G (a), and Diclofenac electrode (b).
1 - Cu wire (conductor cable); 2 - PVC tube; 3 - Alloy of Vud; 4 - Sensor pellet (graphite|IA|TCP)

Experimental

Equipment

All emf measurements were carried out with the following cell assembly:

Ag,AgCl | KCl | test solution membrane internal solution | internal reference electrod with varying [DCF^-] [DCF^-] = $1 \cdot 10^{-2}$ M

A I-160 M model pH mV^{-1} meter with Ag-AgCl reference electrode were used for the measurements of potential difference at 25.0°C.

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 M buffer solutions of pH 2.3–11.7 ranges were freshly prepared.

The freshly prepared aqueous standard solutions ($1 \cdot 10^{-7}$–$5 \cdot 10^{-2}$ mol L^{-1}) of diclofenac were prepared in 0.04 mol L^{-1} of buffer solution (for the study of effect of pH) for analytical purposes.

Buffer solutions (pH 2.3–11.7) 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.

Preparation of ion-pair compound

An ion pair complex of diclofenac with base coloring agent rhodamine 6G was prepared by mixing equal quantities of $1 \cdot 10^{-2}$ mol L^{-1} DICL and $1 \cdot 10^{-2}$ mol L^{-1} of rhodamine 6G. 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.

Preparing the paste

The ion-selective electrode (Fig. 1b) was prepared as follows: a PVC tube (5.0×70.0 mm) 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 rhodamine 6G) 0.02 g plasticizer (DBP, DBS, DOF, DNF or TCP) 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 into the prepared site and dried for 2 h.

When not in use, the electrode was kept immersed in a small volume of 0.01 M sodium diclofenac solution.

Sample preparation

1. Sample Urine. To urine samples (5, 10 and 15 ml) 10 ml of $1 \cdot 10^{-3}$ mol L^{-1} of standard solution of diclofenac sodium salt were added. The ionic strength was maintained with KCl (0.1 mol L^{-1}).

2. Pharmaceutical samples.

2.1. 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).

2.2. 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.

2.3. 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.

Results and discussion

Electrode response

It is a well-know 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 rhodamine 6G were investigated and the results are summarized in Table 1. Significant difference in the potential response of the electrodes was found among the five different solvent mediators that were used.

The electrode made using TCP was selected for carrying out the remaining studies. Its response was fast (3 – 10 s) (Fig. 2), and its stability was checked over a period of 5 months.

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

Plasticize	Slope, mV	Linear range, 10^{-2} mol L^{-1}	Detection limit, 10^{-5} mol L^{-1}
DBP	57 ± 1	0.01–5	3.1
DBS	51 ± 2	0.01–5	4.5
TCP	59 ± 2	0.01–5	3.2
DOF	51 ± 2	0.01–5	4.2
DNF	57 ± 2	0.1–5	16

Note: Average of five determinations.

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

Containing of electrode active substance, %	Slope, mV	Linear range, 10^{-2} mol L^{-1}	Detection limit, 10^{-5} mol L^{-1}
11	56 ± 2	0.01–5	5.9
25	59 ± 2	0.01–5	3.2
36	57 ± 2	0.01–5	1.6
60	53 ± 1	0.01–5	63

Note: Average of five determinations.

Effect of pH

The influence of the pH on the potential response of diclofenac ion selective electrodes was tested using $1 \cdot 10^{-7}$–$5 \cdot 10^{-2}$ mol L^{-1} diclofenac solutions over the pH range of 2.3–11.7. Adjustment of pH was carried out using universal buffer solutions. It is apparent from pH-potential profiles that there is change in potential response. So 6–11 range of pH can be taken as the working pH range of the electrode (Fig. 3). It is one of the main and very important advantages of this diclofenac ion-selective electrode.

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.

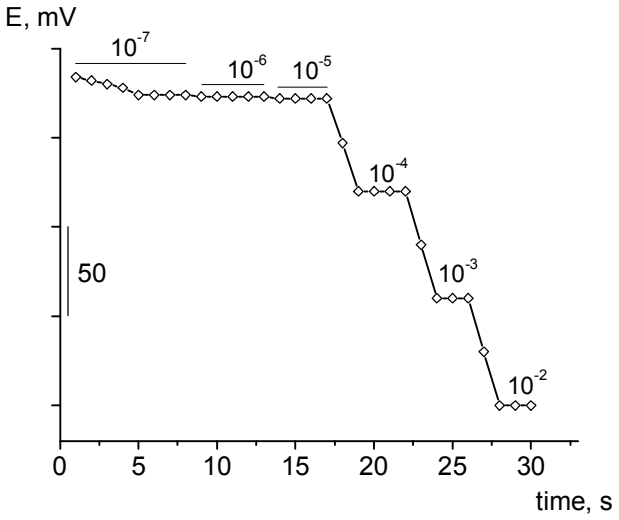


Fig. 2. Response time of diclofenac selective electrode.

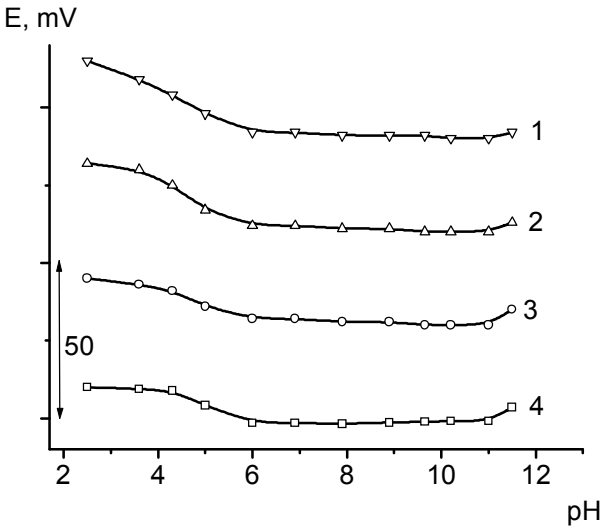


Fig. 3. Effect of the pH of test solution on the potential response of the diclofenac ion-selective electrode (1 – pC 3.3; 2 – pC 3.0; 3 – pC 2.3; 4 – pC 2.0)

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 [25]. 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 endued 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 $-\lg K_{DCF,I}$ are presented in Table 3. Obtained results show that these sensors display sufficiently high selectivity for diclofenac over many common organic and inorganic substances.

No interference was noted for most of the compounds found along diclofenac in pharmaceutical formulations such as glycine, tartrate, glucose, lactose, L-gistidine 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 [19–21]. 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.

Analytical applications

In order to investigate the applicability of the new sensor to the determination of the drugs in the biological fluids, it was used to examine diclofenac content in urine samples and select pharmaceuticals. A 10 ml portion of 0.001 mol L^{-1} diclofenac solution was transferred into

Table 3. Comparison of the selectivity coefficients of the proposed electrode with the reported diclofenac ion selective electrodes

	Ion	Iron(II)-Phtalocyanine, [21]	Complex diclofenac with HDPB, [19]	$Pt\|Hg_2(DFC)_2\|$graphite, [20]	Present work
$-\lg K^{pot}_{DCF,I^-}$	Cl^-	2.3	2.6	0.36	4.6
	Br^-	3.3	3.3	–	4.1
	I^-	2.9	–	–	3.4
	NO_2^-	3.2	–	–	–
	NO_3^-	2.0	2.3	–	2.8
	SO_4^{2-}	3.0	–	3.2	3.8
	SCN^-	3.5	–	–	–
	PO_4^{3-}	3.8	–	–	–
	oxalate	3.8	–	2.1	–
	tartrate	3.6	–	–	4.3
	citrate	3.8	–	–	–
	benzoate	3.3	–	2.1	–
	salicilate	2.7	–	2.0	3.1
	phthalate	3.3	–	2.1	–
	glucose	3.2	2.8	–	3.1
	Mg^{2+}	–	3.2	–	4.8
	Ca^{2+}	–	3.1	–	4.9
	Na^+	–	1.3	–	4.9
	K^+	–	3.0	–	4.7
	glycine	–	2.6	–	4.3
	gistidine	–	–	–	3.7
	lactose	–	–	–	4.2

Note: – wasn't study

Table 4. Comparison of the analytical performance of the proposed electrode with the reported diclofenac ion selective electrodes

Membrane	pH	Slope, mV decade^{-1}	Linear range, 10^{-4} mol L^{-1}	Detection limit, μmol L^{-1}	Resp. time, s	Life time, weeks
Iron(II)-Phtalocyanine, [21]	7.2	-61.0 ± 1.0	0.09–100	5.4	< 10	16
	7.2	-55.0 ± 1.0	0.06–100	4.4	< 5	16
Complex diclofenac with HDPB, [19]	6–9	-59.0 ± 1.0	0.1–600	4.0	< 10	>3
Pt|$Hg_2(DFC)_2$|graphite, [20]	7	-58.1 ± 0.8	0.5–100	32	10–30	20
Ion associate diclofenac with rhodamine 6G	6–11	-59.0 ± 2.0	1–500	35	3–10	20

Table 5. Potentiometric determination of diclofenac in some pharmaceutical formulations (n = 5, P = 0.95)

Sample	Label amount, mg	Found	
		mg	RSD, %
Dicloran® CP tablet	100	99.8 ± 1.4	1.3
Naclofen injectable ampoule	75	75.8 ± 1.1	1.2
Naclofen-ointment	100	101.2 ± 1.5	1.3
Sodium Diclofenac	25.0	26.1 ± 1.4	1.5

Note: RSD = relative standard deviation.

50 ml volumetric flask. After addition of a 5, 10, and 25 ml portion of urine samples, the solution was diluted to the mark with water. The ionic strength was maintained with KCl (0.1 mol L^{-1}). The DCL content of the solution was then determined by the proposed electrode ($3.1 \cdot 10^{-4}$ mol L^{-1}; RSD = 1.5).

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 were then determined by the proposed electrode using the calibration method.

Conclusions

The proposed electrode exhibits long lifetime, good stability, sensitivity, precision, and selectivity. It had rather good metrological characteristics, high sensitivity, and low-cost, easy to prepare and to use. an electrode was developed by us is superior (especially wide pH range of diclofenac determination and lifetime) compared to diclofenac ion-selective electrodes described in other methodologies of its potentiometric determination.

Acknowledgements. This work has been supported by the Ministry of Education and Science of Ukraine and International Visegrad Fund (Grant 997015), the Scientific Grant Agency of the Ministry of Education of the Slovak Republic and the Slovak Academy of Sciences (Grant VEGA No 1/4450/07) and Slovak Research and Development Agency (Project APVV SK-UA-0002-07).

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