April 2007 Volume 5 Issue 1-6

Analytical CHEMISTRY

An Indian Journal

Trade Science Inc.

Full Paper

ACAIJ, 5(1-6), 2007 [119-124]

Determination Of Diclofenac By Membrane Electrode

Corresponding Author

Zholt Kormosh
Volyn State University, Lutsk, (UKRAINE)
E- Mail: kormosh@univer.lutsk.ua

Received: 31st March, 2007
Accepted: 5th April, 2007

Web Publication Date : 15th April, 2007

Co-Authors

Iryna Hunka[1], Raya Krakovyak[1], Iryna Mazurenko[1], Andriy Laganovsky[1] , Yaroslav Bazel[2,3], Nataliya Kormosh[4]

[1]Volyn State University, Lutsk, (UKRAINE)
[2]Uzhgorod National University, Uzhgorod, (UKRAINE)
[3]P.J. Safaric University, (SLOVAKIA)
[4]Lutsk Base Medical College, Lutsk, (UKRAINE)

ABSTRACT

A new diclofenac-selective electrode based on the ion associate diclofenac with basic dye butyl rodamin C as a membrane carrier was developed. The electrode exhibits a good Nernstian slope of 59.0±1.2 mV decade^{-1} and a linear range 5.0×10^{-5} to 5.0×10^{-2} M for diclofenac. The limit of detection was 3.2×10^{-5} M. It has a fast response time 2-3 s and can be used for more the three months. The selective coefficients were determed and this electrode can be used in the pH range 8- 11. The analytical results obtained by applying the proposed method compared very favorably with whose obtained by the Ukrainian Pharmacopoeia standard procedure. This membrane electrode was successful applied for the determination of diclofenac in pharmaceuticals and urine samples.

KEYWORDS

Diclofenac;
PVC membrane sensors;
Potentiometry;
Pharmaceutical analysis.

INTRODUCTION

Diclofenac(Figure 1a), chemically know as 2-[(2,6-dichlorophenyl)amino] benzene-acetic acid monosodium salt, (DIKL) is used in the treatment of many diseases, such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, nonartricular rheumatism[1].

Several types of analytical procedures have been proposed for the analysis of diclofenac in pharmaceutical formulation. These procedures include potentiometry[2-4], fluorimetry[5-7], high-performance liquid chromatography(HPLC)[8], gravimetric[9], partial least squares(PLS)[10-13] and other methods.

Potentiometric methods with ion-selective membranes electrode(ISE's) can provide valuable and straightforward means of assaying diclofenac in pharmaceutical formulations because of the possibility fast and precise determination of the active ions in the solution. ISE's low-cost, easy of use and maintenance, and the simplicity and speed of assay procedure, and the reliability of the analytical information make them very attractive for an assay of pharmaceutical products.

In this work, the preparation of a simple and low-cost electrode is described. The investigated of the experimental variables that the contribute to the elec-

Full Paper

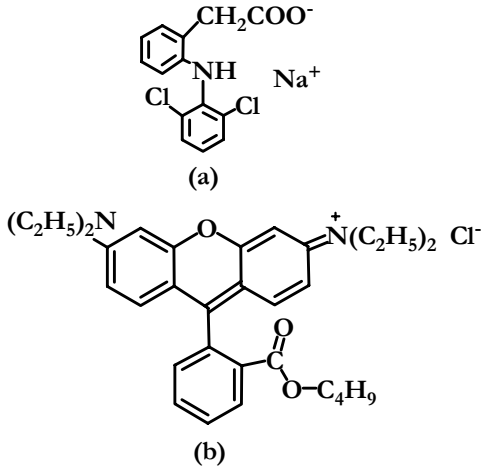

Figure 1: Chemical structure of the sodium diclofenac (a) and butyl rodamin C (b)

trode response led to the development of a simple, selective and reliable methods for diclofenac determination. Studies on the determination of diclofenac in pharmaceutical formulations, particularly capsules dosage formulations and ointments were carried out to illustrate the feasibility of the proposed method.

EXPERIMENTAL

Reagents

All chemicals were of analytical-reagent grade. Distilled water was used to prepare all solution and in all experiments. Dibutylphtalate(DBP), dibutylsebacenate(DBS), dioctylftalate(DOF), dinonilftalate (DNF), tricrezilphosphate(TCP), cyclohexanone (CHN), tetrahydrofuran(THF), high molecular weight PVC were obtained from Sigma-Aldrich. The 0.04 M universal buffer solutions of pH 2.5-11.5 range were freshly prepared.

The freshly prepared aqueous standard solutions(1×10^{-7}-5×10^{-2}M) of diclofenac were prepared in 0.04 M of universal buffer solution(for the study of effect of pH) for analytical purposes. Universal buffer solutions(pH 2.5-11.5) were prepared by mixing corresponding of mixture 0.04 M H_3BO_3, 0.04 M CH_3COOH, 0.04 M H_3PO_4 and 0.2 M NaOH. The ionic strength was adjusted with 0.1 M KCl.

Pharmaceutical preparations

The following commercial dosage forms were analyzed with new ion-selective electrode: Dicloran® CP tablets(India) labeled to contain 100.0 mg of diclofenac(sodium salt) per tablet, sodium diclofenac(Ukraine) labeled to contain 25.0mg of diclofenac(sodium salt) per capsule, dicloberl retard (Germany) labeled to contain 100.0mg of diclofenac (sodium salt) per capsule. Naclofen(Slovenia) labeled to contain 75.0 mg of diclofenac(sodium salt) per ampole.

Determination of diclofenac in pharmaceuticals and urine samples

The analytical products were purchased locally or directly from the manufactures and all were tested prior to the listed expiration date. Four pharmaceutical formulations containing diclofenac salt and other components were analyzed with the diclofenac-sensitive electrode.

1. For pure form

A freshly prepared 5×10^{-2}M aqueous of solution of diclofenac(standard substance) was used as the stock solution. Next solutions(50ml) of diclofenac 1×10^{-7}-1×10^{-2}M were prepared by suitable dilution of the stock solution with water. The ion strength of the final solutions used for the potentiometric determination was kept constant at 0.1M by addition of potassium chloride.

2. Liquid sample

The contents of nine vials were mixed. An aliquot, equivalent to three vials, was transferred to a 50 ml volumetric flask and the volume completed with potassium chloride(the ion strength of solution was 0.1M KCl) and the proposed ion-selective electrode using a calibration graph determined the diclofenac contents. The procedure was repeated five times and was validated by the potentiometric titration methods[1].

3. Solid samples

Fifteen tablets were weight to calculate the average tablet weight. They were finally powdered and homogenized. A portion of the powdered equivalent to about 225.0mg of diclofenac was accurately weighed and dissolving with 40ml of water. The resulting mixture was filtered and ionic strength was adjusted to 0.1M with KCl. Finally, this solution was diluted with water in 50 ml flask and analyzed under

the same procedure described for diclofenac in pure form. This procedure was repeated 5 times.

4. Urine samples

Urine samples were prepared next follows. Before breakfast 5 healthy volunteers received tablet(1×100 mg Dicloran® CP; India). Urine samples were collected in the individual flasks after 5 hours of drug administration and analyzed using a method of standard addition. The aliquots 10, 30, 50ml of urine samples were transferred to 100ml volumetric flasks and 10ml 1×10^{-2} M of standard addition of diclofenac sodium was added and the volume completed with potassium chloride(the ion strength of solution was 0.1 M KCl); the proposed ion-selective electrode was used for the determination of diclofenac in urine samples.

Electrode preparation and conditions

An ion associate diclofenac with butyl rodamin C(Figure 1b) was preparing by mixing of equal quantities of 1×10^{-2} M diclofenac sodium and 1×10^{-2} M of basic dye(butyl rodamin C). The solution was settled during 2 hours and sediment of ion associate was filtered(quantitative rapid filter paper). This residue was treated with 50ml cold distillate water. The filter paper containing the precipitate was dried for 24 h at room temperature. This ion associate diclofenac with butyl rodamin C was used as an electrode active substance for preparing of ion-selective electrode for diclofenac determination.

The general procedure to prepare the membrane electrodes was to mix thoroughly 0.1 g of powdered PVC and 0.04g of ion associate of diclofenac and butyl rodamin C with 0.08ml of DBS as a solvent mediator in 5ml CHN(in some cases THF). The resulting mixture was transferred into a glass dish of 2.5 mm diameter. The solvent was evaporated slowly at room temperature. The thickness of the membrane after drying was 0.5 mm. The diclofenac membrane of 5 mm diameter was cut out and stick into the polyethylene tube by using 10% solution of PVC. A solution 1.0×10^{-2} M (in some cases 5.0×10^{-2} M) of diclofenac sodium was used as internal reference solution.

Instruments

All emf measurements were carried out with the following cell assembly. A I-160 M model pH/mV meter with Ag-AgCl reference electrode were used for the measurements of potential difference at 25.0 ± 0.1^{0}C. The standard procedure of the Ukrainian State Pharmacopeia employed for the assay of diclofenac in pharmaceuticals was utilizes a potentiometric titration method using 0.1 M chloride acid in glacial acetic media[1].

The pH of the solutions was adjusted with a 'AKVILON' (RUSSIA) pH electrode(Model ES-11.7).

RESULT AND DISCUSSION

The influence of membrane composition

It is a well know that the membrane composition have some influence for the sensitivity and selectivity of electrode. So we studied contents of ion associate diclofenac with butyl rodamin C in the membrane and different solvent mediators on the response of electrode proposed and the results are summarized in TABLE 1 and the corresponding emf responses are shown in figure 2. As seen, among the four different solvent mediators, which were used some significant difference on the potential response was founded. The best result was shown by electrode with dibutylsebacenate(DBS) as a solvent mediator and 43% of ion associate content used.

Effect of pH

The influence of pH(Figure 3) on the electrode was tested on the pH range 2.5-11.5 for the 5×10^{-3} and 1×10^{-3} M diclofenac ion concentration. The resulting solutions' pH(s) were adjusted with diluted universal buffer solutions.

For pH values below 7, progressive formation and precipitation of free diclofenac acid, protonation of the secondary amino group of the diclofenac to form cationic species and interference by $[H^{+}]$ cause potential fluctuation.

For pH >11, the hydroxide ion interferes with the electrode response. The emf values are independent of pH in the range 8-11; this can be taken as the working pH range of the electrode.

Response time and lifetime of the electrode

The response time of the electrode was tested

Full Paper

TABLE 1: Effect of membrane composition on the response of ion-selective diclofenac electrode (response time 2-3 s)

Content of IA, %	Solvent mediator	Solvent	The concentration of internal reference solution (mol l^{-1})	Slope (mV)	Linear range (mol l^{-1})	Detection limit (mol l^{-1})
18	DBP	CHN	1×10^{-2}	60±1.0	1×10^{-4} - 5×10^{-2}	1.0×10^{-4}
43	DBP	CHN	1×10^{-2}	61±1.2	1×10^{-4} - 5×10^{-2}	1.0×10^{-4}
43	DBS	CHN	1×10^{-2}	59±1.2	5×10^{-4} - 5×10^{-2}	3.2×10^{-5}
43	TCP	CHN	1×10^{-2}	65±1.2	1×10^{-4} - 5×10^{-2}	5.0×10^{-5}
43	DOP	CHN	1×10^{-2}	38±1.1	5×10^{-4} - 5×10^{-2}	3.2×10^{-5}
43	DNP	CHN	1×10^{-2}	44±1.2	1×10^{-4} - 5×10^{-2}	5.6×10^{-5}
60	DBP	CHN	1×10^{-2}	64±1.1	5×10^{-3} - 5×10^{-2}	1.0×10^{-4}
18	DBP	THF	1×10^{-2}	63±1.0	5×10^{-4} - 5×10^{-2}	2.0×10^{-5}
18	DBP	THF	5×10^{-2}	62±1.0	5×10^{-4} - 5×10^{-2}	2.0×10^{-5}

Note: Average of five determinations

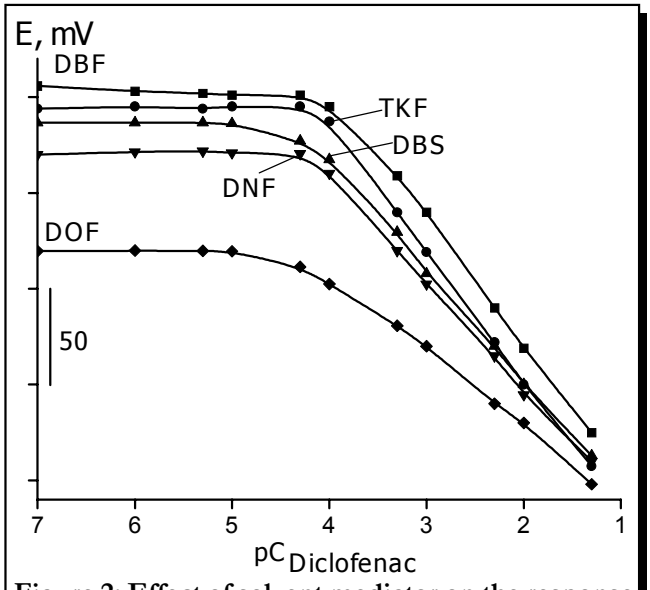

Figure 2: Effect of solvent mediator on the response of the electrode proposed(43% of ion associate content used)

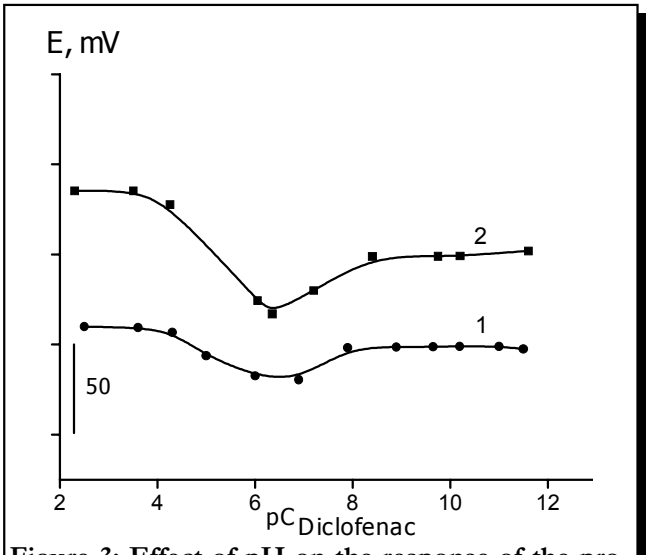

Figure 3: Effect of pH on the response of the proposed diclofenac-selective electrode(1-5×10^{-3}, 2-1 ×10^{-3} M of diclofenac sodium; DBS as a solvent mediator and 43% of ion associate content was used)

by measuring the time required to achieve a steady state potential, for 1×10^{-7}-5×10^{-2}M sodium diclofenac. The electrode yielded steady potentials within 2-3 s at high concentration(>1×10^{-4}M) and about 7 s at concentration near the detection limit. Detectable loss of performance characteristics has not been found after using the electrode up to 3 month.

The influence of the concentration of internal solution on the potential response of the diclofenac-selective electrode was studied and the results showed the concentration of the internal solution doesn't cause any significant difference in the potential response of the electrode, expected change in the intercept of the resulting Nernstian plots(Figure 4).

Electrode response

Over the concentration range 5×10^{-4}-5×10^{-2} M of diclofenac in the calibration solution, the electrode potential response was linear with the concentration of diclofenac(E=-213, 38972+57, 75713 p[DIKL]).

The calibration curve slope was 59.0±1.2 mV p$[DIKL]^{-1}$ and the detection limit was 3.2×10^{-5} M. For calibration curve the optimized electrode with DBS as a solvent mediator and 43% of ion associate

Full Paper

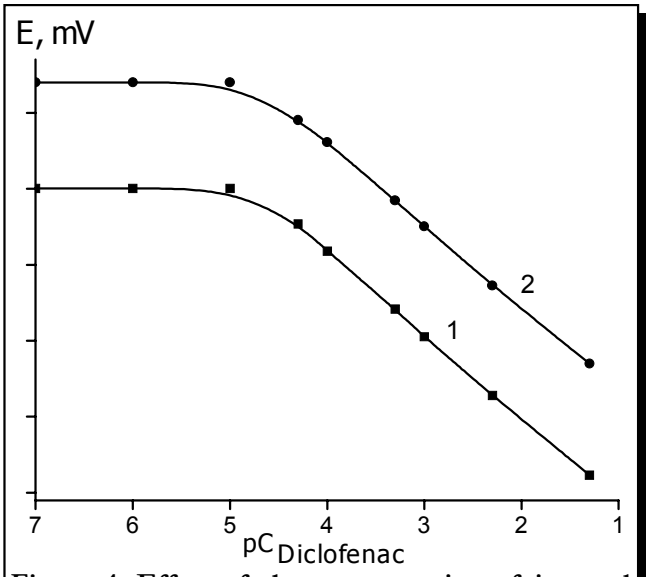

Figure 4: Effect of the concentration of internal solution on the potential response of the diclofenac -selective electrode(1-1×10^{-2}, 2-5×10^{-2} M of diclofenac sodium; DBS as a solvent mediator and 18 % of ion associate content was used)

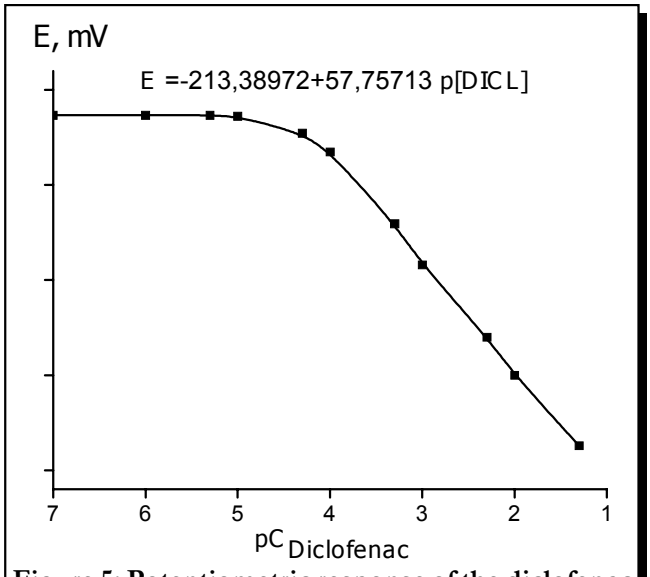

Figure 5: Potentiometric response of the diclofenac -selective electrode to diclofenac using optimized membrane electrode(calibration curve); DBS as a solvent mediator and 43% of ion associate content was used)

content was used. The potentiometric response characteristics of the plasticized PVC-based electrode, incorporating ion associate of diclofenac with butyl rodamin C, towards diclofenac ion is shown in figure 5.

Selectivity of the electrode

The most 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 for membrane diclofenac selectivity electrode $-\lg K^{pot}_{DICL,A}$ were determined, for a number of anions and kations.

The results in TABLE 2 show that the selectivity of the diclofenac ion-selective electrode toward all tested organic anions is good. No interference was noted for most of the compounds found along diclofenac in pharmaceutical formulations such as glycine, tartrate ion, glucose, lactose, L-gistidine and others.

TABLE 2: Selectivity coefficient of various interfering ions for diclofenac-selective electrode(DBS as a solvent mediator and 43% of ion associate content was used)

Ion	$-\lg K^{pot}_{DICL,A^-}$
Mg^{2+}	No interference
Ca^{2+}	No interference
Na^{+}	No interference
K^{+}	No interference
Cl^{-}	No interference
Br^{-}	2.8
I^{-}	0.7
NO_3^{-}	1.5
ClO_4^{-}	0.9
Benzoate	1.9
Glucose	No interference
Salicylate	2.7
Cl-salicylate	2.7
Aspirin	1.7
Tartrate	No interference
Glycine	No interference
Gistidine	1.2

Analytical application

Application of the proposed sensor based on the ion associate diclofenac with butyl rodamin C for quality control of the pharmaceutical preparations was shown. Also this sensor was successful applied for the determination of diclofenac in urine samples. The recovery from five replicate measurements was found to be 4.6×10^{-3} M, RSD=1.4.

TABLE 3 shows the results of proposed method for diclofenac determination in pharmaceuticals (ointments and tablets). The diclofenac content of

Full Paper

TABLE 3: Recovery data for diclofenac spiked in pharmaceutical preparations(electrode with DBS as a solvent mediator and 43 % of ion associate content was used)

Sample	Label amount	Found by proposed electrode		Found by potentiometric tiration[1]	
		Mg	RSD (%) (n=5)	Mg	RSD (%) (n=5)
Dicloran® CP (India)	100.0 tablet^{-1}	102.3±1.8	1.4	103.7±1.4	1.1
Dicloberl retard (Germany)	100.0 capsule^{-1}	101.1±2.0	1.6	101.1±1.5	1.2
Sodium Diclofenac (Ukraine)	25.0 capsule^{-1}	26.8±0.4	1.1	26.0±0.4	1.1
Naclofen (Slovenia)	75.0 ampoule^{-1}	73.4±0.8	0.9	73.7±0.8	0.9

these solutions were then determined by the proposed electrode, using the calibration method.

It has a good agreement with the label amounts and standard method of potentiometric titration of diclofenac ion.

CONCLUSION

The proposed electrode exhibits long lifetime, good stability, and sensitivity, precision, accuracy and selectivity. It is low cost and simple to use. Its usefulness for diclofenac determination in real samples, particularly for some commercial pharmaceutical preparations was demonstrated suggesting its use as a reliable and advantages alternative to the most other previously reported methods in the routine control of diclofenac concentration in these samples.

ACKNOWLEDGMENTS

The authors are gratefully to Ministry of Education and Science of Ukraine(Grant No. M/177-2006) and Ministry of Education of Slovak Republic(Grant No. APVV SK-UA-00806) for providing financial assistance to undertake the work.

REFERENCES

[1] The Ukrainian State Pharmacopoeia, Kharkiv, Sci.Exp.Pharm.Center, 672 **(2004)**.
[2] M.Shamsipur, F.Jalali, S.Ershad; J.Pharm.Biom.Anal., **37**, 943-947 **(2005)**.
[3] A.O.Santini, H.R.Pezza, L.Pezza; Talanta, **68**, 636-642 **(2006)**.
[4] S.S.M.Hassan, W.H.Mahmoud, M.A.F.Elmosallany, M.H.Almazzooqi; J.Pharm.Biom.Anal., **39**, 315-321 **(2005)**.
[5] J.A.Arancibia, M.A.Boldrini, G.M.Escandar; Talanta, **52**, 261-268 **(2000)**.
[6] P.C.Damiani, M.Bearzotti, M.A.Cabezon, A.C.Olivieri; J.Pharm.Biom.Anal., **20**, 587-590 **(1999)**.
[7] L.A.Carreira, M.Rizk, Y.El-Shabrawy, N.A.Zakhari, S.S.Toubar; J.Pharm.Biom.Anal., **13**, 1331-1337 **(1995)**.
[8] C.Arcelloni, R.O.Lanzi, S.Pedercini, G.Molteny, at all; J.Chromatography B., **763**, 195-200 **(2001)**.
[9] M.Tubino, R.L.de Souza; J.AOAC International, **88**, 1684-1687 **(2005)**.
[10] M.M.Sena, Z.F.Chaudhry, C.H.Collins, R.J.Poppi; J.Pharm.Biom.Anal., **36**, 743-749 **(2004)**.
[11] J.Chasemi, A.Niazi, S.Ghobadi; Pharm.Chem.J., **39**, 671-675 **(2005)**.
[12] S.Mazurek, R.Szostak; J.Pharm.Biom.Anal., **40**, 1235-1242 **(2006)**.
[13] J.Ghasemi, A.Niazi, S.Chobadi; J.Chin.Chem.Soc., **52**, 1049-1054 **(2005)**.