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Determination of diclofenac in pharmaceuticals and urine samples using a membrane sensor based on the ion associate of diclofenac with Rhodamine B

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Abstract: The potentiometric response characteristics of a diclofenac selective electrode, based on ion association in different plasticizers, were compared. The sensitivity, working range, detection limit and selectivity of membrane sensors demonstrated significant dependence on the type of plasticizers. The potentiometric unit presented a linear response toward diclofenac concentrations between $1 \times 10^{-5} - 5 \times 10^{-2}$ mol L^{-1}, with slopes of approximately 60 mV dec^{-1}, and exhibited a response time of 3 s. The potentiometric analysis of sodium diclofenac in pharmaceutical formulations was perfomed by the membrane electrode proposed and compared with the results of potentiometric titration given by the Pharmacopoeia of Ukraine.

Keywords: Diclofenac, potentiometry, membrane sensor, pharmaceutical preparations

1 Introduction

Diclofenac sodium (Figure 1 (a)) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. These properties are primarily achieved by its ability to block the enzyme cyclooxygenase, but also by an additional direct effect on hyperalgesia due to the functional down regulation of sensitized peripheral pain receptors. The efficacy of diclofenac equals that of many newer and established NSAIDs. As an analgesic, it has a fast onset and a long duration of action. Compared to other

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NSAIDs, diclofenac is well tolerated and rarely produces gastrointestinal ulcerations or other serious side effects. Thus, diclofenac can be considered as one of few non-steroidal anti-inflammatory drugs of first choice used in the treatment of acute and chronic, painful and inflammatory conditions [1].

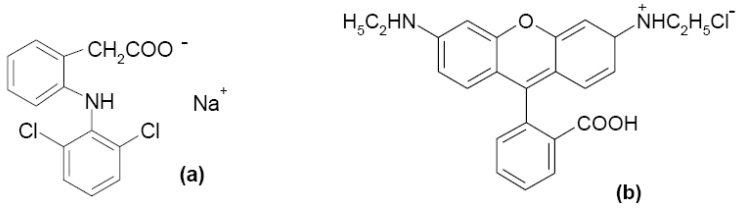

Fig. 1 (a) - diclofenac, (b) - Rhodamine B.

Several methods for the determination of diclofenac in pharmaceuticals and biological fluids have been reported. They include potentiometry [2–4], chromatography [1, 5], fluorometry [6–8], gravimetric [9], spectrophotometric [10–14], chemometric [15–17] and other methods [18–21].

A potentiometric method with ion selective electrodes can provide a valuable and straightforward means of assaying diclofenac in complex mixtures, because it makes possible the direct determination of ions in solution with high selectivity. Most ion selective electrodes are low-cost; their use and maintenance are simple and assay procedures involving such electrodes are generally simple and rapid. These features, coupled with the reliability of the analytical information, make ion selective electrodes attractive for the assay of pharmaceutical products [3].

In this research, the preparation of a simple and low-cost electrode based on ion association between diclofenac and the basic dye, Rhodamine B, is described. Basic dyes are often used as reagents for the extractive spectrophotometric and potentiometric determination of many species [22–24]. Rhodamine B is used as a reagent for extraction-photometric determination of some inorganic elements. However, the problem of determining organic substances using basic dyes has not received proper attention in pharmaceutical analysis. Some organic substances that have an anionic nature can form IA complex with the basic dyes [22]. That property can be applied to the ionometric determination of diclofenac using a membrane sensor based on the formation of an ion associated species of diclofenac with Rhodamine B. Therefore, interest was triggered to conduct a detailed study of conditions and peculiarities of the creation of ionic associates of diclofenac with this base dye. Investigation of the experimental variables that contribute to the electrode response led to the development of a simple, selective and reliable method for assaying diclofenac. This application of analytical chemistry holds much promise.

2 Experimental

2.1 Materials

All chemicals were of analytical-reagent grade. Distilled water was used to prepare all solution and in all experiments. Dibutyl phtalate (DBP), dibutyl sebacate (DBS), dioctyl phtalate (DOF), dinonil phtalate (DNF), tricresyl phosphate (TCP), cyclohexanone (CHN), tetrahydrofuran (THF), high molecular weight polyvinylchloride (PVC) were obtained from Sigma-Aldrich. Buffer solutions (0.04 mol L^{-1}) ranging from pH $2.5 - 11.7$ were freshly prepared.

For the study of the effect of pH, freshly prepared aqueous standard solutions ($1 \times 10^{-7} - 5 \times 10^{-2}$ mol L^{-1}) of diclofenac were prepared in 0.04 mol L^{-1} of buffer solution. Buffer solutions (pH $2.5 - 11.5$) 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 ion associate of diclofenac with Rhodamine B (Figure 1 (b)) was prepared by mixing equal quantities of 1×10^{-2} mol L^{-1} diclofenac sodium and 1×10^{-2} mol L^{-1} of Rhodamine B. The solution was allowed to stand for 2 hours and the ion associate that precipitated was filtered using a rapid, quantitative filter paper. The residue was treated with 50 ml of cold distilled water. The filter paper containing the precipitate was dried for 24 h at room temperature. The ion associate of diclofenac with Rhodamine B was used as an electrode active substance for preparing the membrane of the 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 necessary amount of ion associate of diclofenac and Rhodamine B with necessary volume of a plasticizer in 5 ml cyclohexanone (in some cases tetrahydrofuran). The resulting mixture was transferred into a glass dish 2.5 cm in diameter. The solvent was evaporated slowly at room temperature. The thickness of the membrane after drying was 0.5 mm. A circle, 5 mm in diameter, of the diclofenac membrane was cut and glued to the polyethylene tube using a 10% solution of PVC. A solution of sodium diclofenac, $1.0 \times 10 - 2$ mol L^{-1} or, in some cases, $5.0 \times 10 - 2$ mol L^{-1}, was used as an internal reference solution.

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

A freshly prepared, aqueous solution of diclofenac standard, 5×10^{-2} mol L^{-1}, was used as the stock solution. Additional solutions of diclofenac, 50 ml $1 \times 10^{-2} - 1 \times 10^{-7}$ mol L^{-1}, were prepared by suitable dilution of the stock solution with water. The ion strength of the final solutions used for potentiometric determination was kept constant at 0.1 mol L^{-1} using potassium chloride solution.

Liquid samples: the contents of nine vials (3 ml) were mixed. An aliquot, equivalent

to three ampoules, was transferred to a 50 ml volumetric flask and the volume completed with potassium chloride (the ion strength of solution was 0.1 mol L^{-1} KCl). The concentration of diclofenac was determined with the ion-selective electrode, A calibration graph was prepared. The procedure was repeated five times and was validated using potentiometric titration [1].

Solid samples: fifteen tablets were weighed to calculate the average tablet weight. They were subsequently powdered and homogenized. A portion of the powder equivalent to 225.0 mg of diclofenac was accurately weighed and dissolved in 40 ml of water. The resulting mixture was filtered and the ionic strength of the solution was adjusted to 0.1 mol L^{-1} with KCl. Finally, this solution was diluted with water in a 50 ml flask and analyzed using the same procedure described for diclofenac in the pure form. This procedure was repeated 5 times.

Urine samples: urine samples were prepared as follows. Before breakfast 5 healthy volunteers received a tablet 1×100 mg Dicloberl retard Urine samples were collected in individual flasks 5 hours after administration of the drug. The samples were mixed and analyzed using the method of standard addition. Aliquots, 10, 30, and 50 ml of urine, were transferred to 100 ml volumetric flasks and 10 ml of a 1×10^{-3} mol L^{-1} solution of diclofenac sodium were added. The samples were diluted to volume using potassium chloride, the ionic strength of which was 0.1 mol L^{-1} KCl, and 5 ml of buffer solution (pH 6.5). The ion-selective electrode prepared in this research was used for the determination of diclofenac in urine samples.

2.2 Instrument

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

3 Results and discussion

The nature of the plasticizer plays a fundamental role in determining the potentiometric characteristics of an electrode. Of five different plasticizers employed (dibutyl phtalate, dibutyl sebacate, dioctyl phtalate, dinonil phtalate, tricresyl phosphate), the membrane prepared with DBP (membrane 1) showed the best response characteristics (Figure 2). This membrane consisted of a 25% ion associate of diclofenac with Rhodamine B, 36% DBP, and 39% PVC. The electrode response to diclofenac had a sensitivity of 60 ± 1.0 mV decade^{-1} over the range $5 \times 10^{-4} - 5 \times 10^{-2}$ mol L^{-1} at pH $8.5 - 11.6$, and the detection limit was 5.0×10^{-6} mol L^{-1} (Table 1). Therefore, this membrane was used for detailed measurements. The following electrochemical cell was used:

Ag, AgCl|KCl(std)|test solution|membrane|internal solution|internal reference electrode

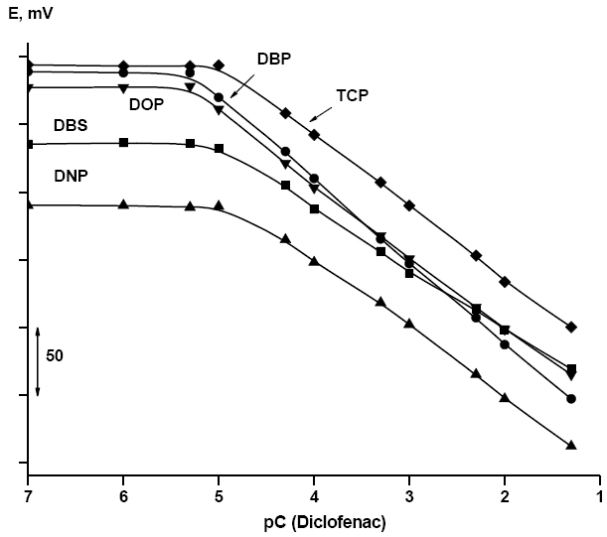

Fig. 2 Effect of the nature of plasticizers on the response of the proposed electrode (the membranes №1, 3 - 6 were used; pH 6.5) at different DCF^- concentrations.

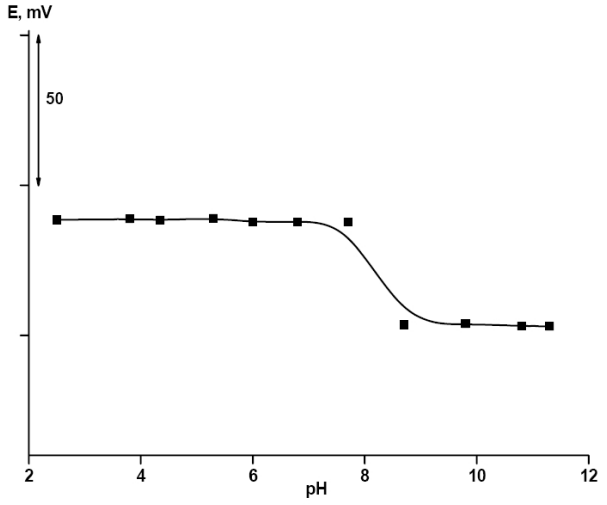

Fig. 3 Effect of the pH of test solution on the potential response of the DCF ion selective electrode (membrane 1), $[DCF^-] = 1 \times 10^{-2}$ mol L^{-1}.

The influence of the content of the ion associate of diclofenac with Rhodamine B on the response of the electrodes prepared was investigated. Some significant differences in the potential response were determined among the various concentrations of the ion associate tested, i.e. 9%, 15%, 25%, 35%. The best result was demonstrated by the electrode prepared with dibutyl phthalate (DBP) as a plasticizer and a concentration of 25% of ion associate.

The dependence of the electrode potential response on pH was studied over the pH

range of 2.4 − 11.6. The ionic strength of the test solution was adjusted using 0.1 mol L^{-1} of KCl. The potential–pH profile for a concentration of 5×10^{-3} mol L^{-1} of diclofenac, illustrated in Figure 3, indicateed that the potential remained constant over the pH ranges of 2.4 − 7.5 and 8.5 − 11.6.

Figure 4 shows the effect of the internal standard solution concentration on the potential response electrode. Sodium diclofenac concentrations of 1×10^{-2} and 5×10^{-2} M were used. Concentration variation of the internal standard solution did not produce any significant differences in the corresponding potential response; however, the overall emf of the cell used was changed. No variation in the slope or detection limit was observed when a,dilute internal reference solution was used. Hence, a diclofenac sodium solution of 1×10^{-2} mol L^{-1} was used as an internal solution to promote smooth functioning of the electrode membrane.

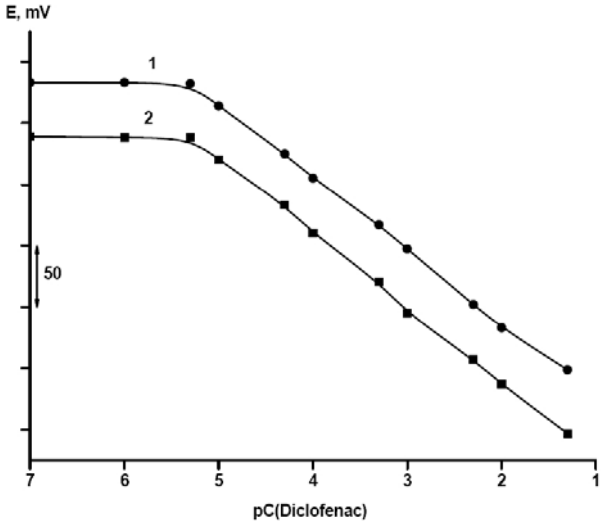

Fig. 4 Effect of the concentration of internal reference solution on the response of the diclofenac-selective electrode prepared: (1 − 1×10^{-2} mol L^{-1}, 2 − 5×10^{-2} mol L^{-1} of sodium diclofenac; membrane 1; pH 6.5).

The dynamic response time of a membrane electrode is an important factor for analytical applications. The response time of the electrode was recorded by changing the sodium diclofenac concentration over a concentration range of $1 \times 10 - 7 - 5 \times 10^{-2}$ mol L^{-1}. The electrode was determined to reach its equilibrium response in 2 − 3 s. The potential of 60 ± 1 mV was obtained for a 1×10^{-2} mol L^{-1} solution of diclofenac in ten successive measurements over 16 weeks. The slope and dynamic range of the electrode during this period remained unchanged. The reproducibility of the electrode was also examined by immersing the electrode alternatively in 1×10^{-2} mol L^{-1} and 5×10^{-2} mol L^{-1} of sodium diclofenac solutions.

The emf response of the membrane, at varying concentrations of diclofenac, indicated a rectilinear range existing from 5×10^{-5} to 5×10^{-2} mol L^{-1}. The slope of the calibration curve was 60 ± 1 mV decade-1 of sodium diclofenac concentration (membrane 1). The detection limit, as determined from the intersection of the two linear segments of the

calibration graph, was 5×10^{-6} mol L^{-1}. The calibration curve is shown in Figure 5.

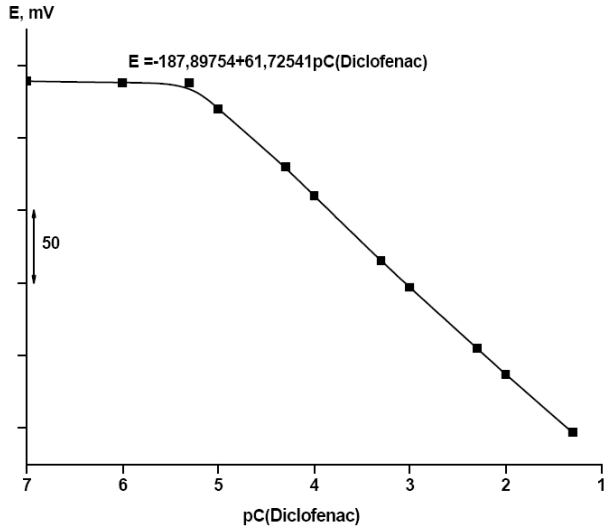

Fig. 5 Calibration plot for the proposed diclofenac selective electrode with optimized membrane composition (membrane 1; pH 6.5).

Selectivity is an important characteristic of an electrode which determines whether a target species concentration can be estimated accurately by using the proposed electrode. The selectivity coefficients of the electrode were determined using the separate solution method [25]. The potentiometric selectivity, $-lgK^{pot}_{DCF,I^-}$, of the membrane diclofenac selectivie electrode was determined for a number of anions and cations (Fig. 6). No interference from ions such as Ca^{2+}, SO_4^{2-}, PO_4^{3-}, tartrate, citrate, etc. was recorded.

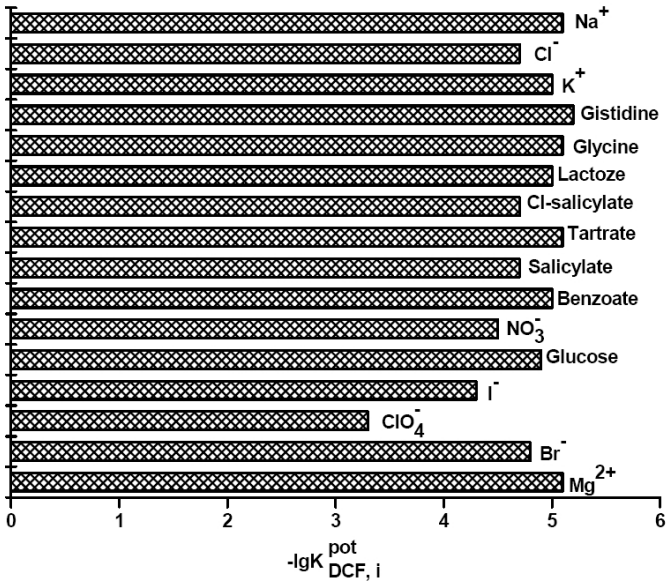

Fig. 6 Potentiometric selectivity coefficients of the diclofenac ion-selective electrode (membrane 1; pH 6.5).

Using the matched potential method, the data in Figure 6 indicated that the ions

investigated did not interfere with the proposed ion selective electrode based on the ionic association of diclofenac with Rhodamine B. 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. Both monovalent ions are treated in the same manner and the valence of the ions does not influence the selectivity coefficient [22].

Table 1 Effect of plasticizer and of the content of ion associate on the response of diclofenac sensitive electrode (response time $2-3$ s; pH 6.5).

Membrane №o	Plasticizer, 36%	Solvent	Concentration of internal reference solution (mol L^{-1})	Slope (mV)	Linear range (mol L^{-1})	Detection limit (mol L^{-1})
1	DBP	CHN	1×10^{-2}	60 ± 1.0	$5\times10^{-5}-5\times10^{-2}$	5.0×10^{-6}
2	DBP	CHN	5×10^{-2}	60 ± 1.2	$5\times10^{-5}-5\times10^{-2}$	5.0×10^{-5}
3	TCP	CHN	1×10^{-2}	52 ± 1.3	$1\times10^{-5}-5\times10^{-2}$	8.0×10^{-6}
4	DOP	CHN	1×10^{-2}	53 ± 1.1	$5\times10^{-5}-5\times10^{-2}$	5.0×10^{-6}
5	DNP	CHN	1×10^{-2}	58 ± 1.1	$5\times10^{-4}-5\times10^{-2}$	1.6×10^{-5}
6	DBS	CHN	1×10^{-2}	46 ± 1.2	$1\times10^{-5}-5\times10^{-2}$	1.0×10^{-5}
7	DBP	THF	1×10^{-2}	58 ± 1.3	$1\times10^{-5}-5\times10^{-2}$	5.3×10^{-6}
8	DBP	THF	5×10^{-2}	59 ± 1.1	$1\times10^{-5}-5\times10^{-2}$	5.3×10^{-6}

Table 2 Comparison of the analytical performance of the proposed electrode with other diclofenac ion selective electrodes reported in the literature.

Membrane	pH	Slope mV decade^{-1}	Linear range, mol L^{-1}	Detection limit, mol L^{-1}	Resp. time, s	Life time, weeks
Iron(II)-Phtalocyanine, [4]	7.2	-61.0 ± 1.0	$9\times10^{-6}-1\times10^{-2}$	5.4×10^{-6}	<10	16
		-55.0 ± 1.0	$6\times10^{-6}-1\times10^{-2}$	4.4×10^{-6}	<5	
Complex diclofenac with HDPB, [2]	$6-9$	-59.0×1.0	$1\times10^{-5}-6\times10^{-2}$	4.0×10^{-6}	<10	>3
Pt|Hg|$_2$(DFC)$_2$|graphite, [3]	7	-58.1 ± 0.8	$5\times10^{-5}-1\times10^{-2}$	3.2×10^{-5}	$10-30$	20
IA diclofenac with Rhodamine B, [this research]	$2.4-7.5$ $8.5-11.6$	-60.0 ± 1.0	$5\times10^{-5}-1\times10^{-2}$	5.0×10^{-6}	$2-3$	18

On the basis of experimental results, we have shown the successful applicability of the new membrane electrode based on the ion associate of diclofenac with Rhodamine B for determining diclofenac in pharmaceutical formulations and urine samples. In Table 4, results for determining the concentration of diclofenac in selected pharmaceuticals are shown. The results are in satisfactory agreement with the labeled amounts. The recovery from five replicate measurements for the determination of diclofenac in urine samples was determined to be 2.7×10^{-4} M, RSD = 1.2.

4 Conclusions

The method presented in this manuscript used a membrane electrode based on the ion associate of diclofenac with Rhodamine B for determination of diclofenac in pharmaceutical preparations and urine samples. The protocol is simple, rapid and low in cost.

Table 3 Comparison of the selectivity coefficients of the proposed electrode with the reported diclofenac ion selective electrodes for membrane No 1.

	Ion	Iron(II)-Phthalocyanine, [4]	Complex diclofenac with HDPB, [2]	$Pt\|Hg\|_2(DFC)_2$|graphite, [3]	Present research
$-lg K^{pot}_{DCF,I^-}$	Cl^-	2.3	2.6	0.36	4.7
	Br^-	3.3	3.3	-	4.8
	J^-	2.9	-	-	4.3
	JO_3^-	3.3	-	-	-
	NO_2^-	3.2	-	-	-
	NO_3^-	2.0	2.3	*	4.5
	SO_4^{2-}	3.0	-	3.9	*
	SCN^-	3.5	-	-	-
	PO_4^{3-}	3.8	-	-	*
	oxalate	3.8	-	2.1	-
	tartrate	3.6	-	-	*
	citrate	3.8	-	-	*
	benzoate	3.3	-	2.1	5.0
	salicilate	2.7	-	2.0	4.7
	phthalate	3.3	-	2.1	-
	glucose	3.2	2.8	*	4.9
	Mg^{2+}	-	3.2	-	5.1
	Ca^{2+}	-	3.1	-	*
	Na^+	-	1.3	-	5.1
	K^+	-	3.0	-	5.0
	glycine	-	2.6	-	5.1
	gistidine	-	-	-	5.3
	benzyl alcohol	-	3.9	*	-
	perchlorate	-	-	*	3.2
	formate	-	-	3.7	-
	acetate	-	-	2.9	-

* - no interference

Table 4 Diclofenac quantities in actual samples determined using the proposed membrane electrode and potentiometric titration method.

Sample	Label amount, mg	Determined by proposed electrode		Determined by potentiometric titration [1]	
		mg	RSD (%) (n=5)	mg	RSD (%) (n=5)
Dicloran® CP (India)	100.0 tablet^{-1}	101.2 ± 1.6	1.3	103.7 ± 1.4	1.1
Dicloberl retard (Germany)	100.0 capsule^{-1}	99.8 ± 1.4	1.1	101.1 ± 1.5	1.2
Sodium Diclofenac (Ukraine)	25.0 capsule^{-1}	25.7 ± 0.4	1.1	26.0 ± 0.4	1.1
Naclofen (Slovenia)	75.0 ampoule^{-1}	74.8 ± 1.1	1.2	73.7 ± 0.8	0.9

This data obtained provided evidence that the new membrane electrode can be used as an effective way of testing the amounts of diclofenac in pharmaceutical formulations and biological fluids.

Acknowledgments

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