AN ION-SELECTIVE SENSOR FOR ASSAY OF DICLOFENAC IN MEDICINES

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A diclofenac-selective electrode with a plasticized polyvinylchloride membrane was developed. The electrode contained an ionic associate of diclofenac with neutral red and its response was linear over the diclofenac concentration range 5×10^{-5} to 5×10^{-2} M with an electrode function slope of (30.0 ± 1.1) - (44.0 ± 1.2) mV/pC. This membrane electrode was used as a sensor for assaying diclofenac in pharmaceutical formulations.

Key words: Diclofenac sodium, selective electrode, polyvinylchloride membrane.

Diclofenac sodium, sodium salt [2-(2,6-dichloroanilino)phenyl]acetic acid (DA) is a non-steroidal anti-inflammatory (NSAID) of the phenylacetic acid derivatives group. It has marked anti-inflammatory, analgesic, and antipyretic actions and decreases tissue edema in inflammation. It is used in rheumatism, rheumatoid arthritis, osteoarthritis, joint disease, and other conditions [1, 2].

Various methods are used for analytical estimation of diclofenac in substances and medicines (tablets, capsules, creams): gravimetry [3], high-performance liquid chromatography [4, 5], spectrophotometry [6 – 11], luminescence [12 – 15], and potentiometry using ion-selective electrodes (ISE) [16 – 19].

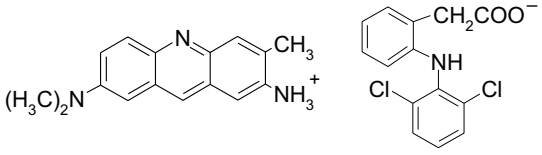
The aims of the present work were to study the possible use of an ion associate (IA) of diclofenac with neutral red as the electrode-active substances in plasticized ISE and to use this to create a new sensor for the estimation of diclofenac in various medicinal formulations.

EXPERIMENTAL SECTION

Starting solutions of the basic stain neutral red (NR) at a concentration of 1×10^{-2} M were prepared by dissolving accurately weighed portions of a commercial preparation in double-distilled water after preliminary purification by recrystallization from methanol. Before dissolution, portions of stain were wetted with a few drops of methanol. The standard 1×10^{-2} M solution of DA was prepared by diluting accurately weighed portions in double-distilled water.

Ion associates of diclofenac and neutral red were prepared by precipitation on mixing 1×10^{-2} M solutions of DA and NR at a ratio of 1:1. The components were mixed and left at room temperature for 2 h. The resulting precipitate was collected by filtration, washed several times with cold distilled water, and dried at room temperature for two days.

A diclofenac-selective electrode for ionometric analysis was developed using polyvinylchloride membranes plasticized with dioctylphthalate (DOP), dibutylphthalate (DBP), dinonylphthalate (DNP), dinonylsebacenate (DNS), tricresylphosphtate (TCP), in which the electrode-active substance (EAS) was an ionic associate of diclofenac and neutral red.



Plasticized polyvinylchloride membranes were prepared as recommended [20].

Potentiometric measurements were performed using an I-160.M ion meter at room temperature; the reference electrode was a standard silver chloride electrode type ÉVL-1MZ. Measurements used the classical electrochemical cell construction.

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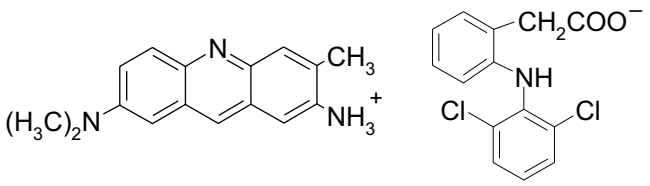

Fig. 1. Effects of solution pH on the response of the diclofenac ISE: *1*) pC 1×10^{-2} M; *2*) pC 5×10^{-2} M.

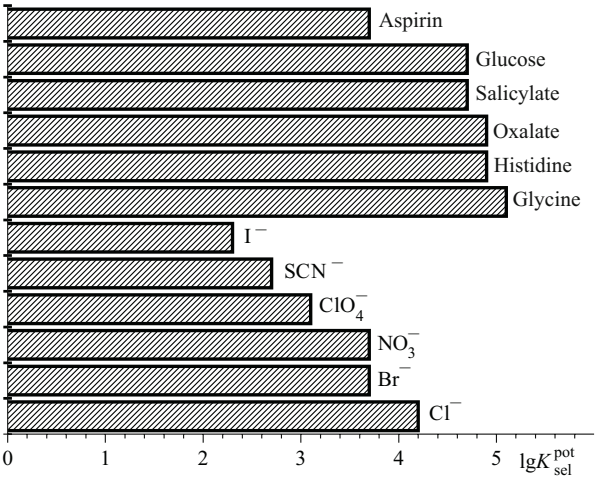

Fig. 2. Potentiometric coefficients of selectivity of the diclofenac ISE.

Ag, AgCl|$KCl_{(sat)}$|study solution|membrane|
(1×10^{-7} to 5×10^{-2} M DA)
|internal solution|Cu
(1×10^{-2} M DA)

The ionic strength of the solution was maintained using 0.1 M KCl solution. The pH values of solutions were maintained with a buffer mixture (0.04 M solution of acetic, boric, or phosphoric acid mixed with 0.2 M NaOH solution) and were measured potentiometrically using a glass electrode.

RESULTS AND DISCUSSION

Studies of the electrochemical properties of the ISE with different contents of the ionic associate provided evidence that all ISE responded to diclofenac concentrations over the wide range of 1×10^{-7} to 5×10^{-2} M. However, the best results were obtained with membranes containing 5 – 20% IA. Increases in the IA concentration led to membrane heterogeneity and degradation of their mechanical and electrochemical properties. The electrode function slope decreased for membranes with IA contents of less than 5%. An important factor influencing the electrochemical properties of the ISE was the plasticizer used in membrane synthesis. In all cases, electrode function was seen over the DA concentration range 5×10^{-5} to 5×10^{-2} M, though the slopes differed for membranes with different plasticizers, ranging from (30.0 ± 1.1) to (44.0 ± 1.2) mV/pC (Table 1).

The effects of various factors on the electrochemical properties of the ISE were studied: pH, the concentration of the internal solution, the response time, potential drift, etc.

These experiments showed (Fig. 1) that the working interval of the electrode was pH 5 – 12, and corresponded to dominance of the single-charged anionic form of DA in the aqueous solution.

Potential drift was no greater than 2 – 5 mV/h. Stable electrode potentials were established over periods of 3 – 10 sec. The membranes synthesized here retained their characteristics for at least four months.

Particular attention was paid to studies of the selectivity of the system. The coefficient of selectivity lgK_{sel}^{pot} relative to various indifferents was assessed in accordance with the IUPAC recommendations using the separate solutions method. The resulting coefficients of selectivity for DA assay in relation to different substances are shown in Table 2.

TABLE 1. Electrochemical Characteristics of ISE for Diclofenac Assay.

EAS content, %	Plasticizer	*S*, mV/pC	$E = f(\log C)$, *M*	c_{min}, *M*
9	DNP	30.0 ± 1.1	$5 \times 10^{-5} – 5 \times 10^{-2}$	2.0×10^{-5}
9	DOP	44.0 ± 1.2	$5 \times 10^{-5} – 5 \times 10^{-2}$	4.0×10^{-5}
9	DBP	39.0 ± 1.1	$5 \times 10^{-5} – 5 \times 10^{-2}$	6.3×10^{-5}
9	TCP	37.0 ± 1.3	$5 \times 10^{-5} – 5 \times 10^{-2}$	1.6×10^{-5}
9	DNS	30.0 ± 1.1	$5 \times 10^{-5} – 5 \times 10^{-2}$	2.0×10^{-5}
5	DBP	38.0 ± 1.2	$1 \times 10^{-4} – 5 \times 10^{-2}$	2.0×10^{-5}
20	DBP	42.0 ± 1.1	$5 \times 10^{-5} – 5 \times 10^{-2}$	4.0×10^{-5}

TABLE 2. Results of Diclofenac Assays in Medicinal Formulations ($n = 5$; $P = 0.95$).

Formulation	Specification, mg	Diclofenac found, mg	Standard deviation, *Sr*
Dicloran® CP	100.0	98.9 ± 1.2	0.01
Dicloberl Retard	100.0	99.4 ± 0.8	0.01
Diclofenac sodium	25.0	25.6 ± 0.7	0.02
Naclofen	75.0	74.2 ± 1.0	0.01
Naclofen	75.0	74.1 ± 1.0	0.01
Naclofen	10.0	9.6 ± 0.6	0.05
Naclofen Duo	75.0	74.2 ± 0.9	0.01
Dicloberl Retard	75.0	74.5 ± 0.7	0.01
Dicloran Plus	10.0	9.2 ± 1.0	0.09

Diclofenac could be assayed in the presence of significant quantities of SO_4^{2-}, PO_4^{3-}, Mg^{2+}, Ca^{2+}, Na^+, and K^+ ions. The ISE developed here was more selective than previously described electrodes for DA assay.

The analytical characteristics of the ISE provided evidence that it was efficient and could be used for analysis of various diclofenac-containing samples, in particular, pharmaceutical formulations.

Assay method. Prior to analysis, samples of diclofenac-containing solutions for injection and gels were dissolved in double-distilled water. Other forms (capsules, tablets) were analyzed after grinding in an agate mortar followed by dissolution in double-distilled water.

The ISE and reference electrode were immersed into the resulting solutions and the electrode potential of the system was measured. Diclofenac concentrations were read from calibration curves or by the added-found method.

Five repeat measurements were performed in each case ($p = 0.95$) and analysis results were determined statistically (Table 2).

Thus, the present studies demonstrated that the ionic associate of neutral red and diclofenac can be used as an EAS for a diclofenac-selective electrode. The operating conditions for the proposed sensor were studied (effects of solution pH, nature of plasticizer, diclofenac concentration, response time, electrode lifetime, etc.). The selectivity of the ISE for diclofenac was assessed. The results provided the basis for the development of a new, sensitive, selective, and simple potentiometric assay for diclofenac, whose application to various pharmaceutical formulations was verified.

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