

Potentiometric diclofenac detection in wastewater using functionalized nanoparticles



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ABSTRACT

Ion selective electrodes for diclofenac monitoring in both pharmaceutical wastewater and dosage form were described; that are considered environmental friendly analytical method. The sensors development depended on comparative performance evaluation of membranes that were based on functionalized magnetite nanoparticles with the classical sensors; this approach provided that nanoparticles in the inner solution of sensor membrane were highly dispersed and coated with ionophore to enhance a complete ion-pairing interaction between the ionophore and the analyte. The optimum membrane was that containing β -cyclodextrin coupled with magnetite ferric oxide as inner filling solution, dibutylphthalate as plasticizer and crystal violet as ion exchanger in poly (vinylchloride) matrix. This sensor (CV-Fe- β -CD) exhibited high sensitivity, Nernstian slope of the calibration curve, as well as fast, stable response and good selectivity. The sensor exhibits a Nernstian slope of -58.7 ± 1 mV/decade over the concentration range 1.0×10^{-7} to 1.0×10^{-2} M of Diclofenac with a minimal limit of detection of 1.1×10^{-7} M. The electrode showed a good potentiometric selectivity for diclofenac with respect to a number of interfering ions and organic species. The membrane sensor was successfully applied for the determination of diclofenac in wastewater samples and dosage form without sample pretreatment steps prior to its analysis.

1. Introduction

One of the major goals of environmental chemistry is pharmaceutical analysis, that is due to their presence in aquatic environment after their incomplete removal in wastewater treatment step, either from pharmaceutical manufacturing; that flush the large amount of unused pharmaceutical into water supply in order to clean the machines or the discharge of huge quantities of drugs by households and hospitals to get rid of expired and unused drugs into waterways and also the animals wastes laced with antibiotics and hormones that animals take in order to keep them away from infection and grow faster [1]. Despite of the low concentration levels of those pharmaceutical residues, they affect aquatic life and humans as they may cause several toxic side effects like, change in behavior, inhibition of cell proliferation and reproductive damage. There are many studies shown that, high concentration of antibiotic can make change in bacterial structure so it make resistance to many bacteria and also has a great effect on food chain, that may threat drinking water sources [2]. Diclofenac potassium (DICLO); potassium [*o*-(2,6-dichloroanilino)phenyl] acetate is an aryl acetic acid

non-steroidal anti-inflammatory drug (NSAID), its chemical structures is shown in Fig. 1; is one of the highly detected pharmaceutical in water matrices and can potentially cause deleterious effects on aquatic life [3,4].

Chromatographic methods are the most commonly used analytical technique for tracing of these pharmaceutical residues in waters such as GC-MS [5,6] or LC with ultraviolet detector [7,8] and tandem mass spectrometric detection [8–10]. Although these techniques are very sensitive with low detection limits, but they require the use of organic solvents, expensive apparatus, technicians with high qualifications and also sample treatment is a required step prior to its analysis that is unsuitable for screening tasks purposes.

The potentiometric sensors are recently used for pharmaceutical tracing in the environment as an alternative technologies [11–15], as they have the advantages of being eco-friendly, simple design, provide the portability for *in situ* monitoring and use small amounts of sample as well as providing sensitive and consistent measurements at reasonable costs [16], ion-selective membrane electrodes have been successfully used for both *in vitro* and *in vivo* assays of pharmaceutical products [17],

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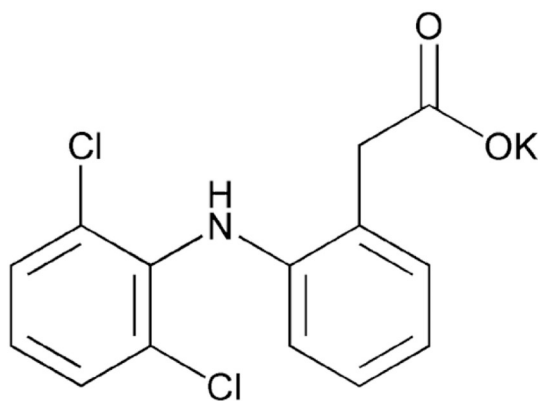


Fig. 1. Chemical structure of diclofenac potassium.

as well as environmental pollutants [18–26].

Various ion-selective electrodes for DICLO detection in pharmaceutical preparation and biological fluids were described either based on using cationic exchangers as iron(II)-phthalocyanine, safranin T, crystal violet, rhodamin B, nickel(II) bathophenanthroline, Fe(III) tetraphenylporphyrin-chloride, Fe(III) tetrakis(pentafluorophenyl)porphyrin-chloride, Manganese (III) porphyrin, neutral dye, 2,4,6-tri(2-pyridyl)-s-triazine iron(II), astraflorin, Basic dye BIK [27–37], β -cyclodextrin [38] or graphite matrix [39]. Only one ISEs were constructed for determination of DICLO in water sample by using imidazolium–diclofenac ion associate in a plasticized poly(vinyl chloride) (PVC) membrane on planar carbon electrodes, with an intermediate poly(3,4-ethylenedioxythiophene) layer [40].

The modification of electrodes is one of the most important developments to increase the drug detection and the electron transfer rate at the electrode surface [41–45], that is why our study deals with the development of a potentiometric approach based on functionalized nano-sized magnetized iron oxide (MNP-Fe₃O₄) particles that were highly dispersed and coated with ionophore and plasticizer to promote an *in situ* cooperative ion-pairing interaction between the ionophore and the analyte present in inner solution of sensor membrane leads to more rapid and sensitive detection of Diclofenac in wastewater samples and pharmaceutical dosage form in the presence of an anionic and organic interfering substances, different types of sensors were constructed using two cationic exchangers as Malachite green (MG) and Crystal violet (CV) with β -Cyclodextrins (β -CD) forming sensors (MG- β -CD), (CV- β -CD), respectively. These sensors were then conjugated with (MNP-Fe₃O₄) forming the respective (MG-Fe (β -CD)) and (CV-Fe (β -CD)) sensors. Those sensors were prepared and fully characterized. The effect of highly dispersed magnetic nano-sized particles coated with host molecule β -Cyclodextrins (β -CDs) on the sensor characteristics was investigated and compared with the traditional potentiometric sensors.

2. Experimental

2.1. Equipment

Potential measurements were made by a Jenway digital ion analyzer model 3505 (Jenway, UK) with Ag/AgCl double junction reference electrode (Aldrich, USA). A Jenway pH glass electrode (Jenway, UK) was used for pH adjustments.

2.2. Chemicals and reagents

All chemicals and reagents used were of analytical reagent grade. High molecular weight polyvinyl chloride (PVC), dibutyl phthalate (DBP), tetrahydrofuran (THF) were obtained from Aldrich, USA. Malachite green oxalate salt (MG) was obtained from alpha chemika. India, Crystal violet (CV) was supplied from Nice chemicals, India, β

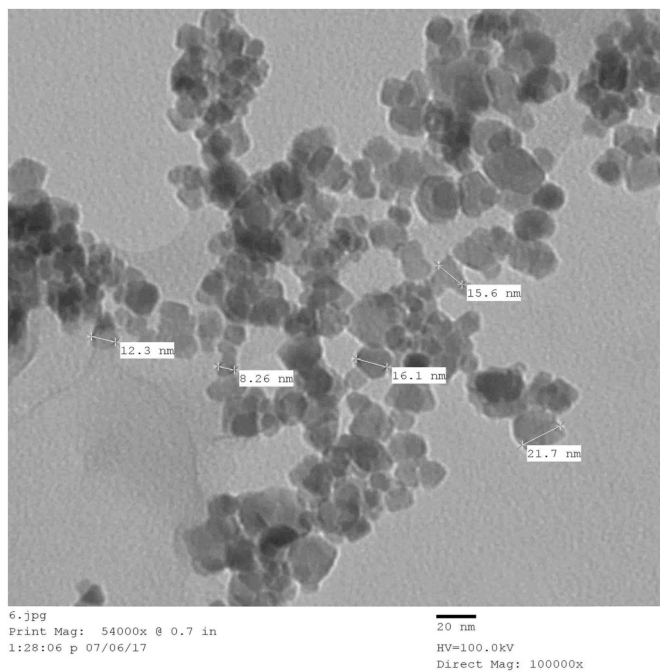


Fig. 2. TEM micrography of Fe₃O₄ nanoparticles.

cyclodextrin was obtained from Euromedex (France), sodium hydroxide scales (NaOH), Hydrochloric acid (HCl), potassium chloride were supplied from El-Nasr company, Egypt, Iron oxide (Fe₃O₄) magnetite nanoparticles (15 nm diameter) were purchased from Nanotech Egypt for photo electronics Co.(Dreamland, 6th October city, Egypt) manufactured by classical precipitation method; its transmission electron microscopy (TEM) micrography is shown in Fig. 2 and diclofenac potassium powder was kindly supplied by GlaxoSmithKline (GSK) and its percentage purity was found to be 99.78 ± 0.81 , using potentiometric titration according to official methods [46].

2.3. Standard solutions

2.3.1. Stock solution

Diclofenac potassium stock solution (1×10^{-2} M) was prepared by dissolving 0.1667 g in potassium dihydrogen phosphate/orthophosphoric acid buffer (pH 7).

2.3.2. Working solutions (1×10^{-3} – 1×10^{-8} M)

Serial dilution of the stock solution using potassium dihydrogen phosphate/orthophosphoric acid buffer of (pH 7).

2.4. Procedures

2.4.1. Water samples collection

Five pharmaceutical wastewater samples were taken from industries at different locations and stored in one liter amber bottles made of glass. Filtration must be done first through membrane filter (0.45 μ m) to get rid of solid particles before their storage at 4 °C to prevent degradation or decay as recommended by the Environmental Protection Agency [47].

2.4.2. Functionalization of iron oxide nanoparticles

Coating of nanoparticles with ionophoric polymer β -CD, by mixing 0.04 g Fe₃O₄ and 0.04 g β -CD dissolved in 0.35 ml DBP, thoroughly added with 5 ml THF solvent till complete consistency in a separate tube, then an ultrasonic treatment was done for 30 min for the formation of a stable magnetic fluid solution. Finally, the magnetic fluid was obtained after the evaporation of the solvent from the mixed solution

room temperature.

2.4.3. Fabrication of membrane sensors

2.4.3.1. Preparation of PVC based membrane sensors (MG-βCD and CV-βCD). Amount of 0.01 g of MG or CV with 0.04 g of β-CD were separately incorporated in 0.19 g PVC plasticized with 0.35 g DBP, respectively in two glass petri dish (5 cm diameter), for the preparation of sensor MG-βCD and MG-Fe (β-CD) then the mixtures were dissolved in 5 ml THF. The petri dishes were left overnight at room temperature to allow THF evaporation. Master membranes with a thickness of about 0.1 mm were formed, disks (≈ 10 mm diameter) were cut from those master membranes with the help of a cork borer and THF to paste it to PVC tips; that were clipped into the end of the electrodes glass bodies. The internal reference solution was made by mixing two equal volumes of 10⁻⁴ M DICLO and 10⁻⁴ M KCl. These sensors were soaked in of 10⁻⁴ M DICLO for 24 h before measurement, at the end Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution acted as an internal reference electrode.

2.4.3.2. Functionalized iron oxide nanoparticles based technique. MG-Fe (β-CD) sensor and CV-Fe (β-CD) sensor were synthesized by the same mentioned procedure under Section 2.4.3.1 except that 20 μl aliquots of the produced Nano sized functionalized Ferro fluids were introduced into the inner reference solution of the membrane electrodes.

2.4.4. Sensors calibration

The prepared sensors were dipped in conjunction with reference glass electrode in 100-ml beakers containing 50 ml of standard DICLO solutions with concentration range of (1 × 10⁻⁸–1 × 10⁻² M), starting from the lowest to the highest concentrations for sensor calibration, with constant stirring using a magnetic stirrer, then the stable potential within ± 3 mV was recorded. The electrode potential response (EMF) was plotted against the logarithm of the DICLO concentration.

2.4.5. pH effect on the EMF response of the suggested sensors

The pH effect on the potential responses of the four studied sensors was tested using 10⁻³ M and 10⁻⁴ M DICLO solutions over pH range of 3–11 at 1 pH interval. The pH was adjusted using either sodium hydroxide or hydrochloric acid solutions. The potential obtained at each pH value was recorded.

2.4.6. Sensors selectivity

The potentiometric selectivity coefficients log K_{pot} (Primary ion, interferent) were evaluated by the separate solutions method [48]. The potentials of 10⁻³ M standard DICLO solution and 10⁻³ M aqueous interferent solutions were measured separately. Potentiometric selectivity coefficients were calculated using the following equation:

$$\log K_{AB}^{Pot} = (E_B - E_A)/S$$

where K_{pot}^{A,B} is the potentiometric selectivity coefficient, E_A and E_B are the emf reading of 10⁻³ M of the drug and the interferent solutions, respectively, S is the slope of the calibration plot (mV decade⁻¹).

2.4.7. Determination of Diclofenac potassium in spiked pharmaceutical water samples

The membrane sensors were immersed in conjunction with the reference electrode in 50-ml beaker containing 45 ml of the collected water samples spiked with 5 ml of 10⁻³ M standard DICLO solution. The concentration of DICLO was calculated from the corresponding regression equation. The pH of these pharmaceutical water samples was adjusted first to 7, to be within the pH working range of the proposed sensors.

2.4.8. Determination of Diclofenac potassium in pharmaceutical dosage form

The contents of five tablets of the drug were finely powdered and an

accurately weighed portion equivalent to one tablet (25–100 mg) was dissolved in about 20 ml of bi-distilled water and then transferred into a 50 ml volumetric flask. The solution was diluted to the mark with potassium dihydrogen phosphate/ortho-phosphoric acid buffer (pH 7). The potential of the sensor was measured and compared with the calibration graph.

3. Results and discussion

One of major problems that face the analyst in the detection of pharmaceutical compounds in wastewater matrices is the sample treatment before analysis, in order to avoid any interference of organic and inorganic contaminants with the analytical procedures. One of the major advantages of ion selective electrodes (ISEs) over other methods, that it do not need sample treatment and that explains its importance for the environmental analysis [49].

Nowadays, magnetite Fe₃O₄ nanoparticles are one of the most popular used nanoparticles in different applications. It's small size, absence of internal diffusion resistance and high surface area to volume ratio, provided better kinetics for the adsorption of substances from aqueous solutions [50], furthermore, the β-CD introduction onto the surfaces of MNP-Fe₃O₄ enhances the dispensability of those magnetic particles in aqueous solutions, increasing their surface area and improving their adsorption capacities [51,52].

3.1. Performance characteristics of the proposed sensors

The evaluation of electrochemical performance characteristics of the investigated DICLO – ion selective electrodes were done according to the IUPAC data [48] as illustrated in (Table 1).

All the sensors gave constant potential readings for day to day measurements, and the calibration slopes did not show changes by more than ± 3 mV/decade over a period of 4 weeks, slopes of sensors (MG-β-CD), (CV-β-CD), (MG-Fe β-CD) and (CV-Fe β-CD) were 57.7, 56.8, 50.3 and 58.7 mV/decade respectively; their calibration plots are shown in Fig. 3. The detection limits of the four sensors were estimated according to the IUPAC definition [48].

As the use of iron oxide nanoparticles was reported to play an important role in the electronic conductivity [53], the “nano” size of the materials will improve their physical properties as the mechanical, electric and electronic properties [54]. By adding the MNP-Fe₃O₄ to the internal reference solution of the sensor, the magnetic particles would be dispersed in the solution rapidly and symmetrically [55]. Once a constant magnetic field was applied, aggregation of this magnetic nanoparticles to the inner side of the membrane leads to better dissolving of the ionophore and the plasticizer adsorbed on the nanoparticles on

Table 1
Electrochemical response characteristics of the investigated membrane sensors.

Parameters	MG-βCD	CV-βCD	MG-Fe (β-CD)	CV-Fe (β-CD)
Slope (mV/decade) ^a	-57.7	-56.6	-50.2	-58.7
Intercept (mV)	80.7	22.2	88.8	61.6
LOD (mol l ⁻¹) ^b	1.1 × 10 ⁻⁵	1.3 × 10 ⁻⁶	1.2 × 10 ⁻⁶	1.1 × 10 ⁻⁷
Response time (s)	10	10	10	10
Working pH range	6–10	7–10	6–10	7–10
Concentration range (M)	10 ⁻² –10 ⁻⁵	10 ⁻² –10 ⁻⁵	10 ⁻² –10 ⁻⁶	10 ⁻² –10 ⁻⁷
Stability (weeks)	4 weeks	4 weeks	4 weeks	4 weeks
Average recovery (%)	100.06	100.07	100.17	100.44
± SD ^a	± 0.88	± 1.65	± 1.61	± 1.34
Correlation coefficient (r)	0.9989	0.9991	0.9992	0.9989

^a Result of five determinations.

^b Limit of detection (measured by interception of the extrapolated arms of Fig. 3).

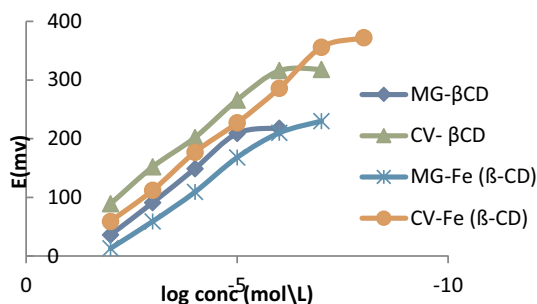


Fig. 3. Profile of the potential in mV to log concentration of Diclofenac using the proposed sensors.

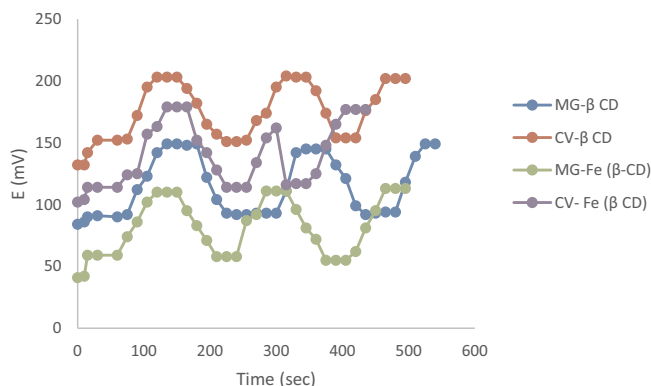


Fig. 4. Reversibility of the proposed sensors in high to low (1.0×10^{-3} to 1.0×10^{-4} M) sample cycle.

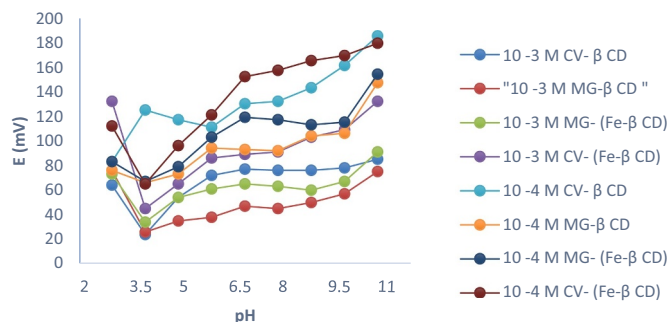


Fig. 5. Effect of pH on the response of the proposed sensors at concentrations 10^{-3} and 10^{-4} M.

Table 2
Potentiometric selectivity coefficients of by separate selectivity method (SSM).

Interferent ^a	Selectivity coefficient ^b			
	MG-βCD	CV-βCD	MG-Fe (β-CD)	CV-Fe (β-CD)
Ibuprofen	1.65×10^{-2}	6.7×10^{-3}	3.98×10^{-2}	1.82×10^{-2}
Paracetamol	2.6×10^{-2}	2.3×10^{-3}	5.24×10^{-2}	0.89×10^{-2}
Chloride	0.14	2.18×10^{-2}	8.7×10^{-2}	5.88×10^{-2}
Phosphate	0.105	1.58×10^{-2}	6.3×10^{-2}	3.98×10^{-2}
Nitrate	8.2×10^{-2}	3.02×10^{-2}	0.128	4.41×10^{-2}
Sulfate	9.3×10^{-2}	2.6×10^{-2}	9.2×10^{-2}	5.6×10^{-2}
Bromide	0.13	2.08×10^{-2}	7.6×10^{-2}	6.45×10^{-2}
Starch	1.99×10^{-2}	3.23×10^{-2}	0.14	1.12×10^{-2}
Acetate	7.8×10^{-2}	4.2×10^{-2}	6.3×10^{-2}	1.5×10^{-2}
Tartrate	7.5×10^{-2}	3.98×10^{-2}	5.72×10^{-2}	3.87×10^{-2}
Oxalate	5.5×10^{-2}	4.76×10^{-2}	6.7×10^{-2}	1.15×10^{-2}

^a Aqueous solutions of 1×10^{-3} M were used.

^b Each value is the average of three determinations.

Table 3
Statistical comparison of the results obtained by the proposed sensors and the official method on pure form.

Items	Official method ^a	MG-βCD	CV-βCD	MG-Fe (β-CD)	CV-Fe (β-CD)
Mean	99.78	100.06	100.1	100.11	100.44
± SD	0.81	0.88	1.65	1.62	1.34
Variance	0.656	0.774	2.74	2.62	1.79
N	5	4	5	5	6
SEM	0.36	0.438	0.704	0.724	0.55
Student's <i>t</i> -test (2.306) ^b		0.498	0.357	0.4045	0.9602
<i>F</i> value (6.3882) ^b		1.184	4.216	4.031	2.789

^a BP method.

^b Figures between parentheses represent the corresponding tabulated values of *t* and *F* at *P* = 0.05.

the surface of the membrane, which yields a significant potentiometric response [56,57], and that explains the best sensitivity of CV-Fe(β-CD) sensor with the use of nanoparticles (magnetite), its linearity range was (10^{-2} – 10^{-7} M), linearity of sensors CV-β-CD and MG-Fe (β-CD) was acceptable as the range was (10^{-2} – 10^{-6} M); while sensors MG-β CD linearity was the least (10^{-2} – 10^{-5} M).

3.2. Response time and reversibility

It is the average required time for the proposed sensors to reach a potential ± 3 mV of equilibrium value. It was recorded by increasing DICLO concentration by 10-fold. It was less than 15 s for the sensors.

The reversibility of the electrode response is important parameters of ion-selective electrodes. In order to evaluate potential reversibility, selected electrodes were immersed repetitively from high concentration of diclofenac potassium salt solution (1×10^{-3} M) to lower concentration (1×10^{-4} M), solutions, the results were shown in Fig. 4. The potentiometric response of the sensors was reversible with longer time to reach the equilibrium as it needed around 1 min (~60 s).

3.3. pH effect on the EMF response of the suggested sensors

The potential pH outline obtained showed that the responses of the sensors MG-βCD and MG-Fe (β-CD) have not been changed over the range 6–10, but for CV-βCD and CV-Fe (β-CD) sensors their working pH range 7–10, results were shown in Fig. 5. As at pH below 5, progressive precipitate formation of the free diclofenic acid and protonation of drug secondary amino group to form cationic species and interference by $[H^+]$ cause potential fluctuation.

3.4. Selectivity of the proposed sensors

From the results showed in (Table 2), it can be seen that sensors CV-βCD and CV-Fe (β-CD) exhibit highest selectivity towards DICLO anion when present with organic compounds and some Inorganic anions that may exists in pharmaceutical dosage forms and expected to be present in wastewater.

3.5. Statistical analysis

Results obtained from the four suggested sensors and the official method were compared and from the calculated values of *t* and *F*, there was no significant difference observed, results shown in (Table 3).

3.6. Potentiometric determination of diclofenac in pharmaceutical water samples

Sensor CV-Fe (β-CD) was applied for DICLO detection in wastewater

Table 4
Determination of diclofenac potassium (Diclo) in wastewater sample by using sensor CV-Fe (β -CD).

Wastewater sample	Drug concentration ^c
W.W 1 ^a	7×10^{-6}
W.W 2	1.6×10^{-6}
W.W 3	1.03×10^{-6}
W.W 4	N.D. ^b
W.W 5	N.D.

^a Wastewater samples.

^b Not detected.

^c Concentration in molarity.

Table 5
Determination of diclofenac^a in some pharmaceutical preparations using sensor CV-Fe (β -CD).

Trade name and source	Nominal content (mg/tablet)	Recovery ^b (%)
Cataflam (Novartis, Egypt) (Batch number Y2274)	25	101 \pm 1.12
Voltaren (Novartis, Egypt) (Batch number Y0095)	50	100 \pm 1.28
Epifenac (EIPICO, Egypt) (Batch number 1608311)	100	98.38 \pm 1.79

^a The active ingredient of all drugs is diclofenac sodium except for cataflam, for which the active ingredient is diclofenac potassium.

^b Average of 3 measurements.

Table 6
Comparison of some electrochemical responses of sensors for DICLO in pharmaceutical preparations.

Ion-pair	Slope	LOD (molar)	pH range	References
Crystal violet	59	2.5×10^{-5}	6–11	[27]
Bathophenanthroline	55	5×10^{-5}	8–12	[28]
Safranin T	47	3.2×10^{-5}	6–12	[29]
Fe III tetraphenyl porphyrin-chloride	59	1×10^{-5}		[30]
Iron II phthalocyanine	63	9×10^{-6}	5.5–9	[31]
Rhodamin B	60	1×10^{-5}	8	[32]
Manganese(III)-tetrakis (3-hydroxyphenyl)porphyrin chloride	59.7	3×10^{-6}	5.5–11.5	[33]
Neutral Red	44	5×10^{-5}	5–12	[34]
2,4,6-Tri(2-pyridyl)-s-triazine iron(II)	56	1×10^{-6}	5.5–9.9	[35]
Astrafloxacin FF	59	5×10^{-5}	9–12	[36]
Basic dye BIK	60	1×10^{-4}	7–11	[37]

sample, as it has the highest sensitivity, reliable, gives stable and accurate results (Table 4).

3.7. Potentiometric determination of diclofenac in pharmaceutical dosage form

The potential was measured using sensor CV-Fe (β -CD) and compared with the calibration curve (Table 5).

The analytical characteristics of the examined sensor against other published methods for Diclofenac analysis in pharmaceutical dosage form were listed in (Table 6). It is superior to most of other reported methods in its sensitivity, the slope and the pH ranges are comparable with the other methods.

4. Conclusion

Ion selective electrode is a green method of analysis; as it reduces the amount of organic waste produced more than other classical analytical technologies, the incorporation of β -cyclodextrin together with magnetite ferric oxide in the inner solution composition enabled the construction of very sensitive sensors with fast response, that are much better than other examined classical sensors and previously reported in literature.

The results of dosage form and wastewater analysis, showed the applicability of the sensors in both quality control and in environmental studies, without the need of sample treatment prior to its analysis, also the high selectivity of the sensors towards organic and inorganic contaminants that may be present in wastewater samples, proved the ability of MG-Fe (β -CD) and CV-Fe (β -CD) sensors for DICLO detected in wastewater complicated matrices.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.microc.2018.10.017>.

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