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Determination of diclofenac in pharmaceutical preparations using a novel PVC membrane sensor

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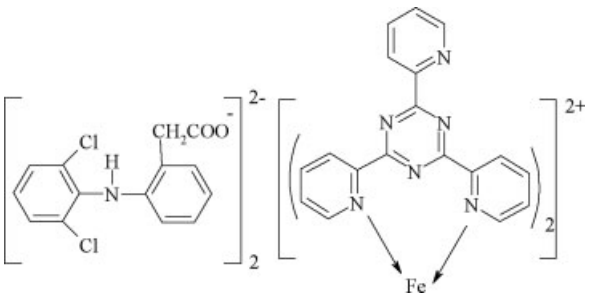
A novel potentiometric PVC membrane sensor for determination of diclofenac in pharmaceutical preparations has been developed. The sensor is based on the use of the 2,4,6-tri(2-pyridyl)-s-triazine iron(II) diclofenac complex [diclofenac-TPTZ-Fe(II)] as an electroactive material in a plasticized PVC membrane matrix. The sensor exhibits fast, stable and near Nernstian response for diclofenac over the concentration range 10^{-2}–10^{-6} M and pH 5.5–9.5. Application to quality control analysis of diclofenac in various dosage forms shows an average recovery of 99% with a mean standard deviation of 0.2%. No significant interferences are caused by inorganic and organic anions and various drug excipients and diluents.

1. Introduction

Diclofenac 2-[(2,6-dichlorophenyl) amino] phenyl acetate is an anti-inflammatory analgesic drug used in the treatment of rheumatic diseases. Several methods have been reported in the literature for the determination of diclofenac in pharmaceutical preparations. These include high performance liquid chromatography [1–6], gas-chromatography [3, 7], thin layer chromatography [8, 9], capillary electrophoresis [10], spectrophotometry [11–15], FT Raman spectrometry [16] and anodic-stripping voltammetry [17]. A potentiometric method based on titration in non-aqueous media has also been described [18]. A potentiometric membrane sensor responsive to diclofenac based on the use of the nickel bathophenanthroline complex has been suggested [19].

It has been reported that some triazine derivatives may be used as ionophores in potentiometric sensors for some cations [20, 21]. Futhermore, 2,4,6-tri(2-pyridy1)-1,3,5-triazine (TPTZ) has been used for the spectrophotometric determination of iron(II) in various complex materials [22].

The present study describes a novel potentiometric membrane sensor for the determination of diclofenac based on the use of the diclofenac 2,4,6-tri(2-pyridy1)-s-triazine-Fe(II) complex as an electroactive material in a PVC matrix membrane. The sensor displays stable and fast response over a wide range of concentrations and pH values. The linear response range and lower limit of detection are at least one order of magnitude better than those previously described [19].



2. Investigations, results and discussion

2.1. Performance characteristics of the sensor

The diclofenac anion reacts with the 2,4,6-tri-2(pyridyl)-1,3,5-triazine-Fe(II) cation to form a stable 2 : 1 water-insoluble ion-association complex (I).

The complex was isolated, characterized and incorporated in a PVC matrix membrane plasticized with either *o*-NPPE or DOP. The membranes were prepared with the composition 2 : 28 : 70 wt% of diclofenac-TPTZ-Fe(II) ion-pair, PVC and plasticizer, respectively. Electrochemical evaluation of the sensors under a static mode of operation was made according to IUPAC recommendations [23]. The performance characteristics of the sensor are given in Table 1. The response curve of a diclofenac-TPTZ-Fe(II)

Table 1: Potentiometric response of diclofenac-TPTZ-Fe(II) PVC membrane sensor

Parameter	Value
Slope, (mV decade^{-1})	-56 ± 1
Intercept, (mV)	-80 ± 1
Correlation coefficient, (r)	0.998
Lower limit of linear range, (M)	5×10^{-6}
Lower limit of detection, (M)	3.4×10^{-6}
Working range, (pH)	5.5–9.5
Response time for 1×10^{-2} M, (s)	15
Life span, (week)	12

membrane sensor incorporating *o*-NPPE displays near-Nernstian response for 1×10^{-2}–1×10^{-6} M diclofenac with an anionic slope of 56 ± 1 (mV decade^{-1}) in 0.1 M $Na_2 SO_4$ background of pH 6.8. The lower limit of detection is 3.4×10^{-6} M diclofenac.

The typical static response time of the TPTZ-Fe(II) based diclofenac sensor is relatively short (<15 s) for (10^{-2}, 10^{-3} and 10^{-4} M) drug solutions. This is observed over a 12 week period, after which the slope and response range tend to decline, probabaly due to leaching of diclofenac-TPTZ-Fe(II) from the membrane.

2.2. Effect of membrane plasticizer

The effect of the solvent mediator on the potentiometric response of the diclofenac-TPTZ-Fe(II)ion − pair complex PVC membrane sensor was examined using two plasticizers of different dielectric constants, *o*-NPPE ($\varepsilon = 24$) and DOP ($\varepsilon = 7$). Membranes plasticized with *o*-NPPE and DOP displayed calibration slopes of −56 and −31 (mV decade^{-1}), respectively. All subsequent measurements were made with sensors with membranes incorporating *o*-NPPE. It has been suggested [24], that no simple rule can account for the change in potentiometric response and selectivity, due to the plasticizer of membranes formulated with ionophores that form complexes with anions. Indeed, it is likely that changes in both single anion partition coefficients and relative anion-ionophore complexation constants can occur with plasticizers of different dielectric constants, and both effects contribute to the final potentiometric response and selectivity of the membranes.

2.3. Effect of pH

The effect of pH on the potential response of the diclofenac-TPTZ-Fe(II) PVC membrane sensor was measured using 10^{-2}, 10^{-3} and 10^{-4} M diclofenac. From the pH-mV profiles, it is evident that the potential readings are constant to within ±0.2 mV over the pH range 5.5–9.5. Within this pH range, diclofenac is completely ionized, dissociated and sensed as a monovalent anionic species. At higher diclofenac concentrations $\geq 10^{-2}$ M, appreciable precipitation of free diclofenac occurs at pH < 5, and the potential sharply increased due to interference by hydrogen ion.

2.4. Effect of foreign ions

Potentiometric selectivity coefficients $k^{Pot}_{dic,B}$ of the diclofenac-TPTZ-Fe(II) PVC membrane sensor were determined using the separate solutions method at 1×10^{-2} M diclofenac and at pH 6.8. The results obtained showed reasonable selectivity toward diclofenac in the presence of many inorganic (e.g., Cl^-, Br^-, I^-, F^-, IO_3^-, SCN^-, PO_4^{3-}, NO_3^-, NO_2^-) and organic (e.g., acetate, formate phthalate, citrate, benzoate, salicylate, tartrate) anions. It can be seen that the selectivity exhibited by the sensor is close with slight deviation from the Hofmeister sequence [25]. Pharmaceutical excipients and diluents commonly used in drug formulations (e.g., glucose, lactose, mannitol and magnesium stearate) at concentrations as high as a 1000-fold molar excess over diclofenac did not interfere. The triazine-Fe(II) complex was also allowed to react with other acidic drugs such as warfarin and ibuprofen. Although an ion-association complex precipitate was formed with warfarin, no such precipitate was formed with ibuprofen. However, sensors incorporating PVC membranes based on triazine-Fe(II) − warfarin and ibuprofen displayed poor response.

2.5. Determination of diclofenac

The validity of the diclofenac PVC membrane sensor for the assay of diclofenac was assessed by determining 0.01–3 mg/ml standards of diclofenac sodium using the calibration graph method. The results obtained displayed an average recovery of 99.6% and a mean standard deviation of 0.4% (n = 4). Diclofenac in different pharmaceutical preparations was similarly determined and the results obtained are listed in Table 2. An average recovery of 99% of the nominal content and a mean standard deviation of 0.3% were obtained. A comparison was also made with results obtained using the standard British Pharmacopoeia [18] method. A close agreement between both results was obtained.

The proposed novel PVC membrane sensor for diclofenac, based on the reaction of the 2,4,6-tri-(2-pyridyl)-s-triazine-Fe(II) ion-association complex with diclofenac, offers a rapid, sensitive, selective and simple method for the direct potentiometric determination of diclofenac in various pharmaceutical formulations without any pretreatment or extraction steps.

Table 2: Determination of diclofenac* in some pharmaceutical preparations using diclofenac-TPTZ-Fe(II) PVC membrane sensor

Trade name and source	Nominal content (mg tablet^{-1})	Recovery** (%)	
		Potentiometry	BP method [18]
Declophen (Pharco Pharma, Egypt)	25	99.3 ± 0.3	96.3 ± 1.7
Voltaren (Swiss Pharma, Egypt)	25	98.5 ± 0.3	97.1 ± 1.1
Voltaren (Swiss Pharma, Egypt)	50	99.1 ± 0.4	96.9 ± 1.8
Voltaren (Swiss Pharma, Egypt)	100	98.5 ± 0.5	98.6 ± 1.8
Cataflam (Swiss Pharma, Egypt)	25	99.0 ± 0.2	96.9 ± 1.8
Diclophenac (El-Nasr Pharma Chem. Co., Egypt)	25	99.8 ± 0.2	98.9 ± 1.5
Diclophenac (El-Nasr Pharma Chem. Co., Egypt)	50	98.9 ± 0.3	97.3 ± 1.5

* The active ingredient of all drugs is diclofenac sodium except for cataflam, for which the active ingredient is diclofenac potassium.
** Average of 3 measurements.

3. Experimental

All reagents were of analytical reagent grade and double distilled deionized water was used throughout. Poly (vinyl chloride), *o*-nitrophenylphenyl ether (*o*-NPPE), and dioctylphthalate (DOP) were purchased from Aldrich Chemical Co. (Milwaukee, USA). Tetrahydrofuran (THF) was obtained from BDH (Poole England) and 2,4,6-tri-2(pyridyl)-s-triazine (TPTZ) was obtained from Sigma Chem. Co. (Mo, USA). Pure diclofenac was obtained from El-Nasr Pharmaceutical and Chemical Co. (Egypt). Dosage forms containing diclofenac were obtained from local drug stores.

3.1. Apparatus

Electrochemical measurements were made at room temperature (25 ± 1 °C) using a Cole-Parmer 5800-50 pH millivoltmeter with the diclofenac membrane sensor in conjunction with a double-junction Ag-AgC1 reference electrode (Orion Model 90-02) containing 10% (W/V) potassium nitrate in the outer compartment. An Orion Research Expandable ion Analyzer EA. 920 with a combination glass electrode (Orion HI 1332) was used for pH measurements.

3.2. Diclofenac TPTZ-Fe (II) ion-association complex

The diclofenac-2,4,6-tri(2-pyridyl)-1,3,5-triazine Fe(II) ion-association complex $[(TPTZ)_2\text{-Fe(II)}][Dic]_2$ was prepared by slow addition of 20 ml of a 10^{-2} M solution of TPTZ to 10 ml of 10^{-2} M iron(II) ammonium sulphate hexahydrate. An intense blue coloured complex was formed due to the formation of a TPTZ-Fe(II) complex. To a 20 ml aliquot of 10^{-2} M diclofenac, 10 ml of a TPTZ-Fe(II) complex were added and stirred well for 10 min. The brown precipitate of diclofenac TPTZ-Fe(II) ion-association complex was filtered off on a G4 sintered glass crucible, washed with double distilled deionized water, dried at room temperature and ground to a fine powder. Elemental analysis data agreed with the composition: $(\text{diclofenac})_2][\text{Fe(II)}(TPTZ)_2]$.

3.3. Diclofenac PVC sensor

Preparation and assembly of the diclofenac sensor were performed as described previously [26, 27]. Diclofenac-TPTZ-Fe(II) ion-association complex (10 mg), *o*-nitrophenylphenyl ether or dioctylphthalate (360 mg) and PVC powder (190 mg) were dissolved in 5 ml THF and mixed in a 5 cm diameter petri dish and equal volumes of 10^{-2} M of diclofenac and 10^{-2} M potassium chloride were used as an internal reference solution. The sensor was conditioned by soaking in 10^{-2} M diclofenac for one day before use and stored in the same solution when not in use.

3.4. Sensor calibration

The sensor is calibrated by transferring 10 ml aliquots of 1×10^{-2}–1×10^{-6} M of diclofenac solution to 50 ml beakers followed by immersing the diclofenac-PVC membrane sensor in the solution in conjunction with a double junction Ag/AgC1 reference electrode. The pH was adjusted to 6.8 by addition of sodium sulphate/sulphuric acid buffer of pH 6.8. The potential readings were recorded after stabilization to $\pm$ 0.5 mV and the e.m.f was plotted as a function of the logarithm of the diclofenac concentration. The calibration graph was used for subsequent determination of unknown concentrations of diclofenac.

3.5. Selectivity coefficient

Potentiometric selectivity coefficients $k^{pot}_{dic,B}$, were evaluated using the separate solutions method according to the following equation [27]:

$$-\log k^{pot}_{dic,B} = \frac{E_B - E_{dic}}{S}$$

where E_{dic} and E_B are the response potentials of the sensor for diclofenac ion and interferent, B, respectively at 10^{-2} M and S is the sensor slope (mV decade^{-1}).

3.6. Determination of diclofenac in pharmaceutical preparations

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 double distilled deionized water and then filtered into a 50 ml volumetric flask. The solution was diluted to the mark with sodium sulphate/sulphuric acid buffer. The potential of the sensor was measured and compared with the calibration graph. Alternatively, the potentials were measured before and after addition of 1.0 ml of 10^{-2} M standard diclofenac solution to the test solution and the unknown concentration was calculated using the standard addition method [27].

References

1 Sane, R. T.; Smant, R. S.; Nayak, V. G.: Drug Dev. Ind. Pharm. **24**, 161 (1986)
2 Li, F.; Cheng, M.: Zhongguo Yaoxue Zazhi **25**, 595 (1990)
3 Chawla, J. L.; Sodhi, R. A. Sane, R. T.: Indian Drugs **33**, 171 (1996)
4 Beaulieu, N. Lovering, E. G.; Lefrancois, J.; Ong, H.: J. Assoc. Off. Anal. Chem. **73**, 698 (1990)
5 Zhang, H. A.; Wang, M. Y.; Wei, Y. X.: Zhang, G. Q.; Sepu, **12**, 376 (1994)
6 Shah, Y. Joshi, S.; Jindal, K. C.; Khanna, S.: Drug Dev Ind. Pharm. **20**, 1303 (1994)
7 Del Puppo, M.; Cighetti, G.; Galli Kienle, M.; Paroni, R.; Borghi, C.: Biol. Mass Spectrom. **20**, 426 (1991)
8 Schumacker, A.; Geissler, H. E.; Mutschler, E.: J. Chromatogr., **181**, 512 (1980)
9 Sun, S. W.; Fabre, H.: J. Liq. Chromatogr. **17**, 433 (1994)
10 Donato, M. G.; Baeyens, W.; Vanden Bossche, W.; Sandra, P. J. Pharm. Biomed. Anal. **12**, 21 (1994)
11 Kamath, B. V.; Shivram, K.: Anal. Lett. **26**, 903 (1993)
12 Kramancheva, I.; Dobrev, I.; Brakalov, L.; Andreeva, A.: Anal. Lett. **30**, 2235 (1997)
13 Bhatia, M. S.; Kashhedidar, S. G.; Chaturvedi, S. C.: Indian Drugs, **34**, 149 (1997)
14 Agrawal, Y. K.; Shivramchandra, K.: J. Pharm. Biomed. Anal. **9**, 97 (1991)
15 Agatonovic- Kustrin, S.; Zivanovic, L.; Radulovic, D.; Vasiljeciv, M.: Analyst **116**, 753 (1991)
16 Davies, M. S.; Binns, J. S.; Melia, C. D.; Hendra, P. J.; Bourgeois, D.; Church, S. P.; Stephenson, P.: J. Int. J. Pharm. **66**, 223 (1990)
17 Wang, E.; Meyerhoff, M. E.: Anal. Chim. Acta **283**, 673 (1993)
18 British Pharmacopoeia, Vol. I Pharmaceutical Press, London 1998
19 Hassan, S. S. M.; Abdel Aziz, R. M.; Abdel Samad, M. S.: Analyst, **119**, 1993 (1994)
20 Huang, D.; Zhang, J.; Zhu, C. Wang, D.; Hu, H.; Fu, T.; Ou, H.; Shen, Z.; Yu, Z.: Huaxue Xuebao **42**, 101 (1984)
21 Huang, D.; Zhu, C.; Zhang, J.; Lei, H.; Wang, D.; Hu, H.; Fu, T.; Ou, H.; Shen, Z.; Yu, Z.: Fenxi Huaxue **12**, 89 (1984)
22 Stephens, B. G.; Felkel, Jr. H. L.; Spinelli, W. M.: Anal. Chem. **46**, 692 (1974)
23 IUPAC, Analytical Chemistry Divison, Commission on Analytical Nomenclature: Pure and Appl. Chem. **67**, 507 (1995)
24 Eugster, R.; Rosatzin, T.; Rusterholz, B.; Aebersold, B.; Pedrazza, U.; Ruegg, D.; Schmid, A.; Spichiger, U. E.; Simon, W.: Anal. Chim. Acta **289**, 1 (1994)
25 Hofmesiter, F., Arch. Exp. Pathol. Pharmacol. **24**, 247 (1888)
26 Craggs, A.; Moody, G. J.; Thomas, J. D. R.: J. Chem. Educ. **51**, 541 (1974)
27 Ma, T. S.; Hassan, S. S. M. Organic Analysis Using Ion-selective Electrodes Vol. 1 Academic Press, London, 1982