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Full Paper

Validation of Selective Electrochemical Method for Determination of Sumatriptan in Combined Dosage Form

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Abstract- A novel sumatriptan (SUM) selective electrode was investigated with dioctyl phthalate as a plasticizer in a polymeric matrix of carboxylated polyvinyl chloride (PVC-COOH), based on the interaction between the drug solution and the dissociated COOH groups in the PVC-COOH. The sensor was fabricated by using PVC-COOH only as anionic site without incorporation of an ionophore. Linear response of SUM within a concentration range of 10^{-6}-10^{-3} M with a slope of 34±1 mV/decade over pH range of 6-8 was observed. The measurement was characterized by a fast stable response within about 45 seconds.The proposed sensor was successfully applied for the selective determination of sumatriptanin the pure powder form and in its pharmaceutical formulation with naproxen without any interference. The results obtained by the proposed procedure were statistically analyzed and compared with those obtained by the U.S. Pharmacopeia method. No significant difference for either accuracy or precision was observed.

Keywords- Sumatriptan, Ion Selective Electrode, Carboxylated PVC, Pharmaceutical Formulation

1. INTRODUCTION

Sumatriptan is 3-[2-(dimethylamino) ethyl]-N-methyl-indole-5-methanesulfonamide as shown in Fig. 1. It is a serotonin agonist acting at the receptors 5-HT1D and 5-HT1B [1-2]. It reduces the vascular inflammation associated with migraine and decreases the activity of the trigeminal nerve, accounts for its efficacy in treating cluster headaches [3- 4].

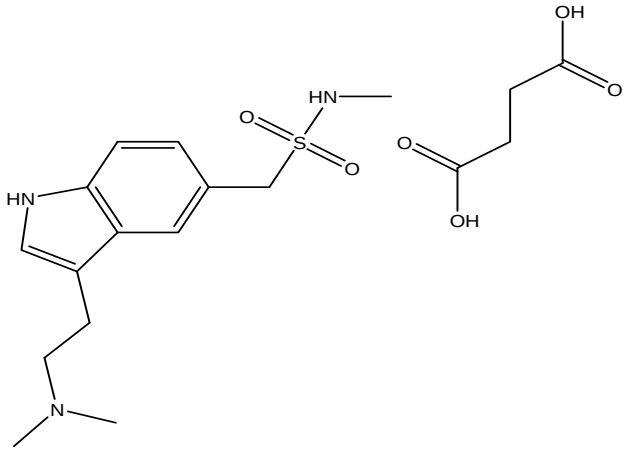

Fig.1. Structural formula of sumatriptan succinate

The literature review revealed several analytical methods for quantitative estimation of SUM in body fluids and in pharmaceutical formulations. These methods include spectrophotometry [5-8], liquid chromatography [9-11], capillary electrophoresis [12] and oxidative voltammetry [13].

In the last three decades, being commercially and not expensive, ion selective electrode technique (ISE) has become an item of general equipment for analytical work and used for selective analysis of many drug products [14-20].

The developed method was successfully applied for the electrochemical determination of SUM in Treximet® tablets. Study of the method selectivity showed that Naproxen is an acidic drug, used as analgesic in combination with SUM, didn't interfere during measurements of pharmaceutical preparation samples due to the basic nature of sumatriptan. The method has the advantages of high accuracy, selectivity and the possibility of direct determination of the drug in turbid and colored solutions.

2. EXPERIMENTAL

2.1. Apparatus

1) Potentiometric measurements were carried out using Jenway, U.K (model 3505) pH/mV meter. A single junction Ag/AgCl reference electrode was used in conjugation with the drug sensor.

2) Bandelin sonorex, RK 510 S, magnetic stirrer
3) Silver wire (3 mm diameter) immersed in the internal reference solution. It was coated with a layer of silver chloride by immersing in a solution of concentrated hydrochloric acid and connecting to the positive pole of a battery while the negative one is connected to a copper wire.

2.2. Materials and reagents

-Sumatriptan pure powder (as succinate): was kindly supplied by Sigma-Egypt. Its purity was found to be 99.24 % according to the official method [9].
-Sumatriptan pharmaceutical formulation: Treximet® tablets (GlaxoSmithKline) was purchased at a local pharmacy (Edmonton, Canada). Each tablet is claimed to contain 85 mg of sumatriptan succinate and 500 mg of naproxen sodium.
-Tetrahyrdofuran (THF) (El Gomhoria Company for Chemicals, Egypt)
-Dioctyl phthalate (DOP) (Sigma, Germany)
-Carboxylated polyvinyl chloride (Sigma, Germany)
-Britton – Robinson (BR) buffer: prepared by mixing the acid mixture containing phosphoric acid (0.04 M), acetic acid (0.04 M) and boric acid (0.04 M). Buffer solutions of different pH values were adjusted by the necessary amount of 0.2 M NaOH.
-Potassium chloride solution (10^{-2} M) for the internal reference solution
-Double distilled water

2.3. Standard solution

Stock standard solution (10^{-2} M) was prepared in 0.1 N HCl by transferring 0.413 g of the drug into 100-mL volumetric flask. 50 mL of 0.1 N HCl was added, shaked for few minutes till dissolve and the volume was completed to the mark with the same solvent. Working solutions of lower concentrations (10^{-7}–10^{-3} M) were prepared by serial dilution using Britton – Robinson pH 6.

2.4. General procedure

2.4.1. Preparation of the membrane sensor

In a glass petri dish (5 cm diameter), 0.35 mL of dioctyl phthalate was mixed with 0.19 g of carboxylated PVC. This mixture was dissolved in 5 mL of THF, covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature forming the master membrane with 0.1 mm thickness.

2.4.2. Electrode assembly

A disk of appropriate diameter was cut from the master membrane and cemented to the flat end of PVC tubing with THF. The membrane was soaked in standard solution of the drug

(10^{-2} M) overnight in order to distribute it in the carboxylated PVC matrix as an ion exchange process.

A mixed solution consisting of equal volumes of 10^{-2} M sumatriptan and 10^{-2} M potassium chloride was used as an internal reference solution. Ag/AgCl coated wire was employed as an internal reference electrode. The sensor was conditioned by soaking for 24 h in 10^{-2} M solution of the drug and stored in the same solution when not in use. The potentiometric cell is presented in Fig. 2.

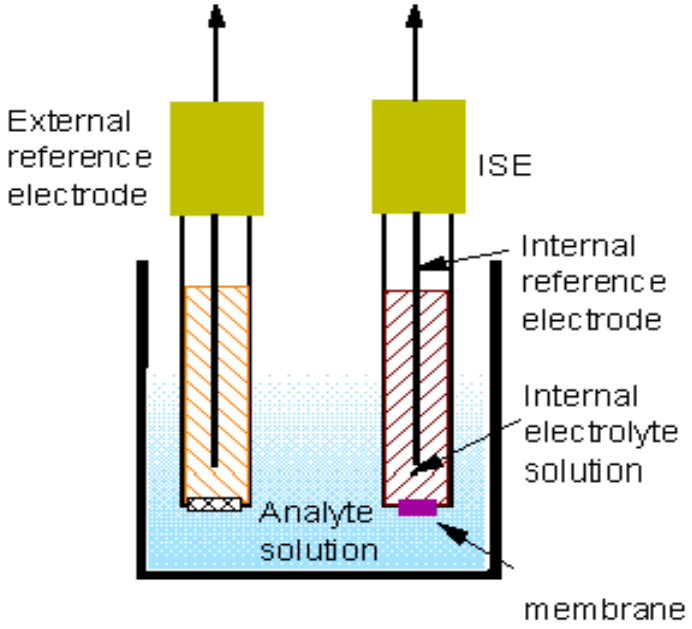

Fig. 2. The potentiometric cell used for the determination of sumatriptan using the proposed ion selective electrode method

2.5. Study of the experimental conditions

2.5.1. Identification of slope, response time and lifetime of the studied electrode

The electrochemical performance characteristics of the studied electrode were evaluated according to IUPAC standards [21]. The slope was computed from the linear part of the calibration graph and the detection limit was taken at the point of intersection of the extrapolated linear segment of the graph.

The dynamic response time of the electrode was tested for the concentrations 10^{-6}–10^{-3} M of sumatriptan solutions. Sensor life span was examined by repeated monitoring of the slope of the drug calibration curve periodically.

2.5.2. Effect of pH on the electrode response

The effect of pH on the potential values of the electrode system was studied over pH range of 4–10 at one pH interval by immersing the electrode in 10^{-4} and 10^{-5} M solutions of the drug. Different values were prepared using Britton–Robinson buffers. The potential obtained at each pH was recorded.

2.5.3. Effect of foreign compounds

The performance of the electrode in presence of interfering substance such as pharmaceutical additives and diluents commonly used in drug formulation was assessed. Selectivity coefficient was calculated by the separate solutions method where 10^{-4} M solutions of naproxen, KCl, NaCl, NH_4Cl, $CaCl_2$, glucose, and lactose were used.

2.6. Application to pharmaceutical dosage form

The content of ten Treximet® tablets were weighed to determine the average tablet weight and then finely powdered. A portion of the powdered tablets equivalent to 0.041 g of sumatriptan succinate was quantitatively transferred to a 100 mL volumetric flask and 50 mL of distilled water were added. The solution was shaken for ten minutes, and the volume was completed to the mark by the same solvent. Tenfold dilution of the previous solution was done using Britton–Robinson pH 6 and the e.m.f produced by immersing the prepared electrode in conjugation with the reference electrode in the prepared solution was recorded. The concentration of sumatriptan was calculated from the regression equation.

3. RESULTS AND DISCUSSION

This work is an attempt to introduce a reliable, sensitive and fast response membrane electrode for the selective determination of sumatriptan. The fabricated PVC sensor mechanism is illustrated whereby sumatriptan acts as a cation in 0.1 N HCl which suggests the use of ion exchanger of the anionic type. The ion-exchange properties of carboxylated polyvinyl chloride relative to neutral carrier-PVC are better due to:

1) The relatively high bulk conductivity of plasticized PVC-COOH compared with plasticized high molecular weight PVC.
2) Higher carrier loading selectivity for PVC-COOH membranes [22].

It is also obvious from the Nernest response of the suggested sensor which was 34±1 mV/ decade that the stoichiometry of the reaction between sumatriptan HCl and carboxylated PVC should be 1:2, respectively. SUM contains acidic nitrogen of the sulphonamide group while the other two amino groups have certain basic property and they can explain the stoichiometric behavior of the reaction. The mechanism can be illustrated as follow:

$$SUM + 2\ PVC\text{-}COOH \longrightarrow PVC\text{-}COO\text{-}\ SUM^{2+}\ \text{-}OOC\text{-}PVC$$

Ion exchange complex

The electrochemical cell of the suggested membrane for the determination of sumatriptan can be illustrated as follow:

Ag/AgCl reference electrode	Test solution	Carboxylated PVC membrane	Internal reference solution	Ag/AgCl internal reference wire

In the present study, DOP plasticizer was used in the fabrication of the proposed sensor. DOP was found to plasticize the membrane and adjusted both the permittivity of the final membrane and the mobility of the exchanger sites. Such adjustments influenced the partition coefficient of the studied drug with subsequent effects on the electrode selectivity.

Electrochemical performance characteristics of the proposed sensor were evaluated according to the IUPAC recommendation data in Table 1. It was found that the electrode displayed constant and stable potential readings from day to day and the calibration slope did not change by more than 2 mV per decade over a period of 2 weeks. The response time of the electrode was tested for concentrations of the drug from 10^{-7}–10^{-2} M. The measurement was characterized by a fast stable response within about 45 seconds.

Table 1. Electrochemical response characteristics of the proposed electrode used for the determination of sumatriptan

Parameter	**Suggested sensor**
Slope (mV/decade)	34 ± 1
Intercept (mV)	265
Response time (seconds)	45
Working pH range	6 - 8
Concentration range (M)	10^{-6} – 10^{-3}
Stability (weeks)	2
Average recovery (%)	101.32
SD	1.23
Correlation coefficient	0.9998

The effect of pH on the electrode potential was investigated and it was found that electrode gave useful pH from 6-8 as shown in Fig. 3. The potentiometric response at the optimum pH was linear with constant slope over a drug concentration range of 10^{-6} – 10^{-3} M as shown in Fig. 4.

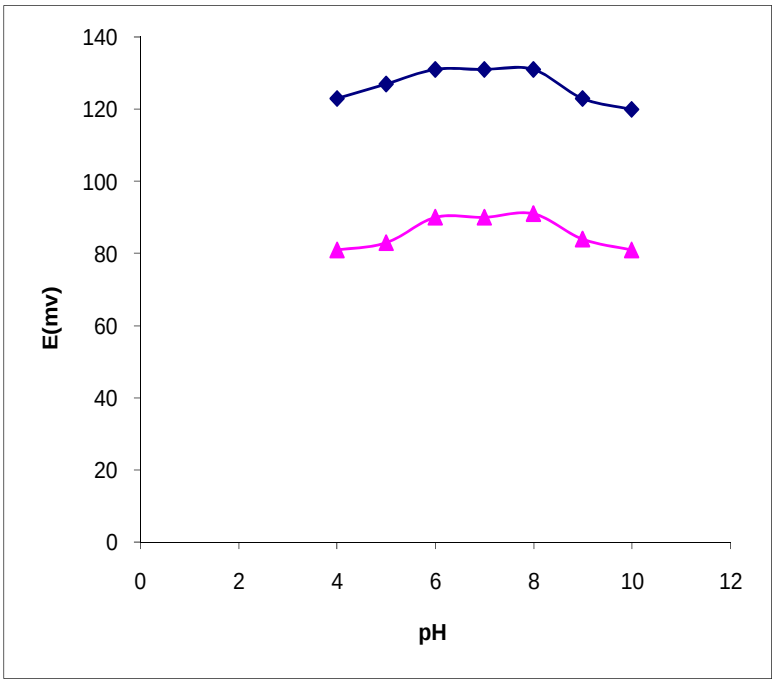

Fig. 3. Effect of pH on the response of proposed electrode

The performance of the electrode in presence of commonly used pharmaceutical additives used in drug formulations (e.g.: naproxen, sodium chloride, potassium chloride, lactose --- etc) was assessed. Selectivity coefficient values ($K^{pot}_{A,B}$) was calculated by the separate solutions method where the potentials were measured for 10-4 M of the drug and then for 10-4 M of the interferent solution, separately. The selectivity coefficients were calculated as shown in Table 2 using the following equation [22]:

$$\log K^{pot}_{A,B} = \frac{(E_B - E_A)}{S} + \left(1 - \frac{Z_A}{Z_B}\right) \log aA$$

Where $K^{pot}_{A,B}$ is the Selectivity coefficient, E_A and E_B are the potentials of the drug and the interferent solutions respectively, S is the slope of the calibration plot , aA is the activity of the drug , Z_A and Z_B are the charges on the drug and the interfering ions respectively.

The accuracy of the proposed membrane sensor for the determination of unknown samples of SUM was assessed. The results showed mean percent recovery of 101.32±1.23 as shown in the validation parameters in Table 3.

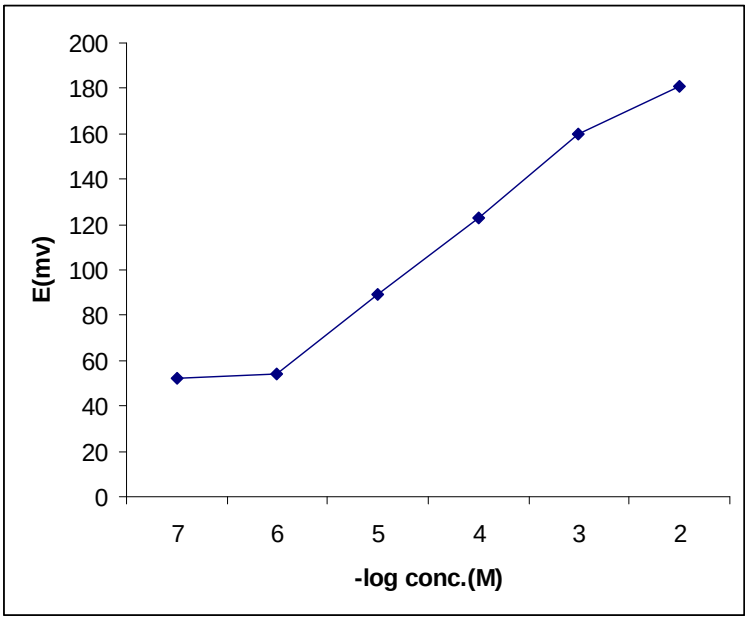

Fig. 4. Profile of the potential in mV to -log concentration of sumatriptan using the proposed ion selective electrode method

Table 2. Potentiometric selectivity coefficients for the proposed electrode used for the determination of sumatriptan

Interferent	**Selectivity coefficient**
Naproxen	4.07×10^{-4}
NaCl	2.45×10^{-3}
KCl	3.92×10^{-3}
$CaCl_2$	5.98×10^{-2}
NH_4Cl	2.91×10^{-4}
Glucose	3.20×10^{-4}
Lactose	5.71×10^{-4}

Table 3. Validation parameters for the proposed electrochemical method for the determination of sumatriptan

Parameter	**Suggested sensor**
Range	10^{-6}–10^{-3} M
Slope	34±1 mV
Intercept	265 mV
Mean	101.32
SD	1.23
Variance	1.51
RSD	1.214
Correlation coefficient	0.9998

Table 4. Determination of sumatriptan in its pharmaceutical dosage form by the proposed electrochemical method

Pharmaceutical formulation	**Taken**	**Mean ± RSD***
Treximet® tablets Batch no. C12470	10^{-4} M	99.50 ± 0.451

* Average of three determinations

The proposed method was successfully applied for the determination of sumatriptan in combined dosage form without any interference neither from naproxen nor the additives as shown in Table 4.

Statistical analysis of the results of analysis of sumatriptan by the proposed electrode and the official method [9] showed no significant difference as shown in Table 5.

Table 5- Statistical comparison between the results of the proposed electrochemical method for the determination of sumatriptan and the official method

Values	Proposed method	Official method*
Mean	101.32	99.24
SD	1.23	0.92
RSD	1.214	0.927
Variance	1.51	0.846
n	5	6
Student's t-test (2.262)**	1.391	
F-value (5.19)**	1.79	

* Official method [9]; HPLC method. The mobile phase consisted of a mixture of phosphate buffer adjusted pH 6.5 and acetonitrile in (3:1, v/v). The chromatographic column used was C18 250×4.6 mm and the detection wavelength was 282 nm.

** Theoretical values of t and F at (P 0.05)

4. CONCLUSION

The use of the developed sensor offers the advantages of fast response, elimination of drug pretreatment or separation steps, selective, low detection limit and direct determination of the drug in turbid and colored solutions. The technique therefore can be used for routine analysis of sumatriptan present in matrix during quality control of pharmaceutical formulations.

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