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Electrochemical sensors for determination of Tranexamic acid in pure form and pharmaceutical preparations

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Abstract
A novel PVC membrane sensor for tranexamic acid based on Tranexamic acid phosphotungstate ion pair complex was prepared. The influences of membrane composition (i.e. percent of ion-pair complex, PVC, kind of plasticizer and ionic additive), inner solution, pH of test solution and foreign cations on the electrode performance were investigated. The optimized membrane demonstrates Nernstian response (56.2 ±0.4 mV per decade) for tranexamic acid cations over a wide linear range from 1.0×10^{-5} to 1×10^{-2} M at 25ºC with lower detection limit 8.0×10^{-6} M. The potentiometric response is independent from the pH of the solution in the pH range of 2.0-4.5. The proposed sensor has the advantages of easy preparation, fast response time. The selectivity coefficients indicate excellent selectivity for tranexamic acid over many common cations (e.g., Na^+, Cu^{2+}, Ni^{2+}, vitamin k_1 and gabapentin). The sensors are used successfully for the determining of tranexamic acid in pure form and pharmaceutical preparations.

Keywords: PVC membrane sensor, tranexamic acid, phosphotungstate, Pharmaceutical preparations

1. Introduction
Chemically Tranexamic acid is trans-4-(aminomethyl) cyclohexane carboxylic acid [1] (Figure 1). It is a synthetic analog of amino acid, lysine [2]. It is a hydrophilic drug and is used as haemostatic and antifibrinolytic agent. Tranexamic acid shows high affinity for lysine binding sites of plasminogen and plasmin [2]. Tranexamic acid acts by being a competitive inhibitor of plasminogen activation. At higher concentration it is a noncompetitive inhibitor of plasmin [3]. It is official in British [1] and European Pharmacopoeia [4].
A literature of survey revealed that there are a few analytical methods have been reported, which include Colorimetric spectrophotometry [5-11], spectroflorometry [12] and HPLC method [13-15] for the estimation of the drug in biological fluids and pharmaceutical formulations.
In the present work, PVC membrane and conventional sensors based on Tranexamic acid-phosphotungestate ion pair complex was introduced for the first time. This facilitate the monitoring of Tranexamic acid down to a small concentrations (8.0×10^{-6} M) either in pure solutions or into pharmaceutical preparations. The sensors exhibited Nernstian slope with fast response time and excellent selectivity towards many organic and inorganic ions.
Although potentiomerty has some advantages over other techniques being easy, precise and accurate, few sensors have been constructed. In the present study new selective membrane electrodes, of plastic membrane type has been constructed for the determination of Tranexamic acid in pure form and pharmaceutical preparations.

2. Experimental Part
2.1 Equipment
All potentiometric measurements were made at 25 ± 1ºC with a Wheeler (Model WD-5010EC) pH/mV meter using Tranexamic acid membrane sensor in conjunction with an Wheeler double junction Ag/AgCl reference electrode containing 10% (w/w) potassium nitrate solution in the outer compartment. A Ross combination pH electrode was used for pH adjustment.

2.2 Chemicals and reagents
All chemicals were of analytical grade. Deionized water was used for all aqueous solutions. Tranexamic acid was kindly supplied by Sigma pharmaceuticals, Quesna city, Egypt. High molecular weight poly (vinyl chloride) powder (PVC), phosphotungstic acid (PTA),***o***-nitrophenyloctyl ether (***o***-NPOE),dioctylphethalate (DOP),dibutylphetalate (DBP), potassium tetrakis(4-chloro-phenyl)borate (KTClPB) and Sodium tetraphenylborate (NaTPB) were purchased from Aldrich. Tetrahydrofuran (THF) was obtained from fluka. Some cation salts of the highest purity were used available.

2.3 Standard drug solution
Stock tranexamic acid solution $1.0x10^{-2}$M was freshly prepared daily by dissolving 0.0393 g of the drug in 25 mL of distilled water. Serial dilutions ($1.0x10^{-6}$-$1.0x10^{-3}$M) were obtained using distilled water. For selectivity measurements the standard solutions were adjusted to pH 3.

2.4 Preparation of ion-pair
The ion-pair was prepared by mixing 50 mL of $1.0x10^{-2}$ M of phosphotungstic acid with an equimolar solution of tranexamic acid, stirred for 10 min. A white precipitate of tranexamic acid-phosphotungstic acid [TXA-PTA] was resulted. This precipitate was filtered and washed thoroughly with distilled water then dried at room temperature for 24 hand ground to fine powder [16, 17]. IR data of TXA, PTA and the TXA-PTA are shown (Figure

2(a)-(c)) to prove the formation TXA-PTA ion pair complex.

2.5 Construction of the sensors

A different amounts of ion-pair with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), and the solution was mixed well into a glass dish of 2 cm diameter. Then, THF was evaporated slowly until an oily concentrated mixture was obtained. Sections of the resulting membrane were cut out with a cork borer (10 mm diameter) and glued to polyethylene tubing. The tube was then filled with internal filling solution consisted of equal volumes of 1 x 10^{-2} M of tranexamic acid and potassium chloride. Several constructions were made to reach to the optimum composition.

2.6 Potential Measurements

Aliquots (25 ml) of 10^{-6} – 10^{-2} M standard solution of tranexamic acid were transferred into 50 ml beakers and [TXA-PTA] sensors in conjunction with reference electrode were immersed in the solution. The solutions were stirred; the potentials were recorded after stabilization and plotted as a function of tranexamic acid concentration these graphs were used for the subsequent determination of unknown concentrations of tranexamic acid.

The life span of the sensor was examined by repeated monitoring of the slope of tranexamic acid calibration curve after soaking different periods (1 day-5 weeks) into 10^{-2} M solution, at 25 °C. The potential reading was recorded after stabilization and the emf was plotted as a function of logarithm tranexamic acid concentration. The detection limit was taken at the point of intersection of the extrapolated linear segments of the tranexamic acid calibration curve. The dynamic response of the sensors was tested by measuring the time required to reach a potential steady to within ± 1 mV after successive immersion of the sensor in different drug solutions each having a 10 fold difference in concentration. The sensors response for different drug concentrations were also tested at various pH values. NaOH and HCl were used for pH-adjustments.

2.7 Selectivity of the Sensor

Selectivity coefficient of the sensor was determined using the separate solution method (SSM) [18] with 10^{-2} M solutions of (TXA) and interferent and calculated from the rearranged Nicolsky equation:

$$log\boldsymbol{K}^{pot}_{TXA,M} = [\boldsymbol{E}_M\text{-}\boldsymbol{E}_{TXA}/S] = log\boldsymbol{a}_M^{(Z_{TXA,M}|Z_M)}+log\boldsymbol{a}_{TXA}$$

Where;

E_{TXA}: is the potential measured in 10^{-2} M tranexamic acid solution.

E_M: is the potential measured in a 10^{-2} M solution of the interfering cations.

S: - slope of the electrode calibration plot.

3. Results and Discussion

3.1 Optimal Sensor Matrices Compositions

Phosphotungstic acid (PTA) $H_3PW_{12}O_{40}$is one of the ionic ionophores used for preparing ion-selective electrodes [19, 20]. The different ionization forms of PTA, at different pH values, facilitate its interaction with many compounds [21]. At pH 1 the ionic species of PTA is $[PW_{12}O_{40}]^{3-}$, pH 2.2 they are $[PW_{12}O_{40}]^{3-}$, $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, at pH 3.5 they are $[PW_{12}O_{40}]^{3-}$, $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, $[P_2W_{18}O_{62}]^{6-}$, $[P_2W_{19}O_{67}]^{10-}$, at pH 5.4 they are $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, $[P_2W_{18}O_{62}]^{6-}$, at pH 7.3 it is $[PW_9O_{34}]^{9-}$, and at pH 8.3 they are PO_4^{3-}, WO_4^{2-}.The interaction between TXA and PTA is based on the interaction between the cationic part of TXA, ammonium group and anionic side of PTA^- as counter ion.

It is well established that each membrane component plays a special role in the membrane function and the sensor response, the sensitivity, linearity and selectivity of the electrode depend significantly on the membrane composition [22] For this purpose, the effects on ISE response according to its composition, inner solution, the presence of interfering ions, the concentration of ion pair in the membrane and polymer content (viscosity) of the membrane were studied experimentally. Nine membrane compositions were prepared, Table 1. The results showed that the electrode made by membrane with 5.0 w% ion-pair 32.0 w% PVC, 62.0 w% *o*-NPOE and 1.0 w% KTClPB exhibited the best performance characteristics (slope 56.2±0.4 mV decade^{-1}) at 25 °Cover tranexamic acid concentration range of 1.0x10^{-5}-1.0x10^{-2} mol L^{-1} with lower detection limit of 8.0x10^{-6} mol L^{-1}.

3.2 Effect of Ion Pair Amount

The amount of ion-pair content in the fabricated electrode matrices was varied from 2% to7%, incorporation of 5% of the TXA-PTA ion-pair was sufficient to the proper performance of the sensor (slope values were 52.5±0.3 mV decade^{-1}).

3.3 Effect of Plasticizer

The prepared ion-pair complex was used as an electro active material in the construction of a new sensor selective for TXA drugs. The ion-pair incorporated in a membrane containing *o*-NPOE, DOP or DBP as plasticizers in PVC matrix and the performance characteristics of the proposed sensor was evaluated according to IUPAC recommendations [23]. Membrane sensors based on TXA-PTA were plasticized with DBP (ε = 4.7), DOP (ε = 7), or *o*-NPOE (ε = 24). They showed calibration graph slopes of 42.8, 43.8 and 52.5 mV per decade with linear ranges of 1×10^{-2} - 5×10^{-4}, 1×10^{-2} - 5×10^{-4} and 1×10^{-2}-$1\times10^{-5}$and lower detection limits of 3.5×10^{-4}, 2×10^{-4} and 1×10^{-5} M, respectively. It can be seen from Table 1 that sensor based on the TXA-PTA with *o*-NPOE plasticized membrane shows highest slope and detection limit than sensors with membranes plasticized with DBP and DOP. This may be due to the highest dielectric constant of *o*-NPOE than DBP and DOP.

3.4 Effect of Ionic Site

It is well known that lipophilic ionic sites promote the interfacial ion-exchange kinetics and decrease the bulk resistance by providing mobile ionic sites in the electrode matrix [24, 25]. The effect of membrane additive was studied by adding different tetraphenylborate derivatives. Addition of (KTClPB) to the electrode matrix exhibited higher slope value compared with NaTPB. The presence of (KTClPB) not only improves the response behavior and selectivity but also enhances the sensitivity of the sensors. Different amount from (KTClPB) was added to the membrane mixture until reach to optimum amount, Table 1.

3.5 Effect of Internal Solution Concentration

The influence of the concentration of internal solution on the emf response of ion selective electrodes was studied. The results showed that variation in the concentration (1×10^{-2} to 1×10^{-4}

molL^{-1}) of the internal solution does not significantly change the electrode response of slope while parameters like measuring range and detection limit [26] changed to considerable extent, Table 2. A 1×10^{-2}mol L^{-1} concentration of internal solution gave the best response.

3.6 Effect of pH

Wide application of an ISE requires the knowledge of the pH range of the functioning of given electrode. The acidity of the medium may affect the state of an ion associate and other membrane components [27]. In order to study the effect of pH on the performance of the sensor, the potentials were determined at two concentrations (1.0×10^{-3}; 1.0×10^{-4} M) of $(TXA)^+$ ions as a function of pH. The pH of the solution was varied by the addition of NaOH and HCl. As it is seen from the results, Figure 4, the potential is independent on the pH changes in the range of 2-4.5. Thus, this range may be chosen as the working pH for the electrodes assembly. At pH <2, the (TXA) cation was protonated, while at pH more than 4.5, the response decreases which may be attributed to decrease in tranexamic acid ion by increasing OH^- concentration.

3.7 Response Time

For analytical applications, the dynamic response time is an important parameter for any sensor [28]. In this study, the practical response time was recorded by changing solution with different concentration from 1.0×10^{-5} to 1.0×10^{-2} M. The actual potential vs. time traces shows that the electrode reaches the equilibrium response in a short time of < 15 s with concentration from 1.0×10^{-5} t5.0×10^{-4} M and 15 s with concentration from $1.0\times10^{-3}$to 1.0×10^{-2} M, figure 6.

3.8 Lifetime

The lifetime of the sensors was detected by measuring the slope of the potential versus (TXA) ion concentration over the concentration range of 5×10^{-6} - 1×10^{-2} M each day over a period of five weeks while the electrodes were in continuous use. The proposed sensor can be used for 4 weeks. After this period there is a slight gradual decrease in the slopes (−2 mV per decade) and the detection limit will increase. It is well known that the loss of plasticizer, (TXA-PTA) complex from the polymeric film due to leaching into the sample is the primary reason for the lifetimes of the sensors, Table 4.

3.9 Selectivity of the Sensor

The potentiometric selectivity coefficient of tranexamic acid sensor was evaluated at different concentrations of both tranexamic acid and the interferents using the separate solution method (SSM) [18]. As it is shown in Table 3. These data reveal that the sensor gave a reasonable good selectivity for TXA as compared to many basic and acidic compounds. No interference were caused by many pharmaceutical expients and diluents commonly used in drug formulations (e.g. enalapril, gabapentin, and glycine).

3.10 Analytical Applications

3.10.1 Determination of tranexamic acid in tablets

The content of five tablets of Tranex or Kapron was finely powdered. An accurate weight of the fine powder equivalent to 0.0393g tranexamic acid was dissolved in 1.0 mL $1.0x10^{-2}$ M hydrochloric acid and filtered off through Whatman filter paper No. 42, the filtrate was completed to mark with distilled water in a 25 mL volumetric flask, shaken well and adjusted at pH = 3 to obtain a solution claimed to contain $1.0x10^{-2}$ M tranexamic acid. Appropriate dilutions were carried out with water to obtain serial concentrations in the range of $1.0x10^{-5}$ - $5.0x10^{-3}$ M to be analyzed using the mentioned sensor.

3.10.2 Determination of tranexamic acid in ampoules

The content of three ampoules of Bledex or Kapron was mixed. 0.5 ml of this mixture was taken then completes to mark with distilled water in a 25mL volumetric flask to obtain a solution claimed to contain $1.0x10^{-2}$Mtranexamic acid. pH adjusted at 3 by using $1.0x10^{-2}$M hydrochloric acid. Appropriate dilutions were carried out with water to obtain serial concentrations in the range of $1.0x10^{-5}$-$5.0x10^{-3}$ M to be analyzed using the mentioned sensor.

The sensor in conjunction with double-junction Ag/AgCl reference electrode was immersed in the volumetric flask of the prepared solutions. The mV of the test solutions were directly measured and compared with the calibration graph. The results for determination of tranexamic acid amount in some pharmaceutical samples from local pharmacy are shown in Table 5. The results are in satisfactory agreement with the stated content on drug

4. Conclusion

The described potentiometric method has simple workup procedure and requires no sophisticated instrumentation. It determines only the therapeutically active undegraded drug in the presence of its excipients without separation. The results obtained also show that the constructed sensor provide response suitable for analytical use in the determination of tranexamic acid in drug bulk powder and some pharmaceutical preparations. Apart from showing linear response with high accuracy and sensitivity, they also have high selectivity, reproducibility and it offers distinct advantages in rapidity and simplicity

Table 1: Optimization of membrane components

Membrane No.	Composition (%)				Slope (mV decade^{-1})	Linear range	LDL (M)
	ion pair	PVC	plasticizer	Add.			
1	2	34	64 ***o***-NPOE	_	50.5	$1x10^{-2}$ - $5x10^{-5}$	$4.5x10^{-5}$
2	3.5	33	63.5 ***o***-NPOE	_	51.1	$1x10^{-2}$ - $5x10^{-5}$	$2.5x10^{-5}$
3	5	32.5	62.5 ***o***-NPOE	_	52.5	$1x10^{-2}$ - $1x10^{-5}$	$1x10^{-5}$
4	7	32	61 ***o***-NPOE	_	51.6	$1x10^{-2}$ - $5x10^{-5}$	$2x10^{-5}$
5	5	33	62 DBP		42.8	$1x10^{-2}$ - $5x10^{-4}$	$3.5x10^{-4}$
6	5	33	62 DOP	_	43.8	$1x10^{-2}$ - $5x10^{-4}$	$2x10^{-4}$
7	5	32	62 ***o***-NPOE	1 *KTClPB*	56.2	$1x10^{-2}$ - $1x10^{-5}$	$8x10^{-6}$
8	5	31	62 ***o***-NPOE	2 *KTClPB*	55.6	$1x10^{-2}$ -$1x10^{-5}$	$9x10^{-6}$
9	5	32	62 ***o***-NPOE	1 NaTPB	51.7	$1x10^{-2}$ -$5x10^{-5}$	$4.8x10^{-5}$

Table 2: Effect of internal solution concentration on electrode performance

Electrode number	Internal solution. conc. (M) mol L $^{-1}$	Slope (mV decade^{-1})	Linear range (mol L^{-1})	Detection limit(M)
7	10^{-2}	56.2	1×10^{-2}-1×10^{-5}	8.0×10^{-6}
	10^{-3}	55.9	1×10^{-2}-1×10^{-5}	1×10^{-5}
	10^{-4}	55.7	1×10^{-2}-5×10^{-5}	2.5×10^{-5}

Table 3: Selectivity coefficient $logK^{pot}_{TXA,M}$

Interferent	Log $logK^{pot}_{TXA,M}$
Na^{+}	-2.39
Cu^{++}	-4.30
Amm. oxalate	-2.28
Benzamide	-2.36
Mg^{++}	-4.89
Ni^{++}	-3.91
Amm. Renieckate	-2.61
K^{+}	-2.46
Glycine	-2.52
Maltose	-4.81
Amm. Citrate	-2.01
Gapabentin	-1.82
Enalapril	-1.94
Phylloquinone (Vitamin k_1)	-1.97

*****The results based on five measurements.

Table 4: Lifetime of PVC membrane electrode

Week	Slope (mV decade^{-1})	LDL (mol L^{-1})
First	56.2	$8.0x10^{-6}$
Second	55.9	$9.0x10^{-6}$
Third	55.4	$1.5x10^{-5}$
Fourth	54.7	$2.5x10^{-5}$
Fifth	52.2	$8x10^{-5}$

Table 5: Determination of tranexamic acid in its pharmaceutical preparations

Sample	Stated content in drug	Found *	According to British pharmacopoeia
Bledex	100mg/ml	99.23% ±0.13 %	99% to 101%
Kapron	500mg/5ml	99.35% ±0.22 %	
Kapron	500mg/tablet	99.07% ±0.2 %	
Tranex	500mg/tablet	99.11% ±0.15 %	

Table 6: Potentiometric response characteristics of the best membrane

Parameter	Membrane number (6)*
Slope (mV decade^{-1})	56.2
Lower detection limit (LOD)	8×10^{-6}
Correlation coefficient (r) (n=5)	0.997
Linear range	1.0×10^{-2}-1×10^{-5}
Working pH range	2-4.5
Life span (week)	4

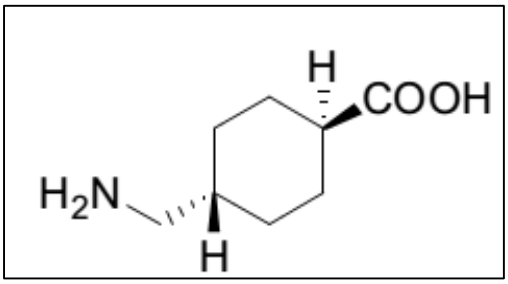

Fig 1: Structure of tranexamic acid

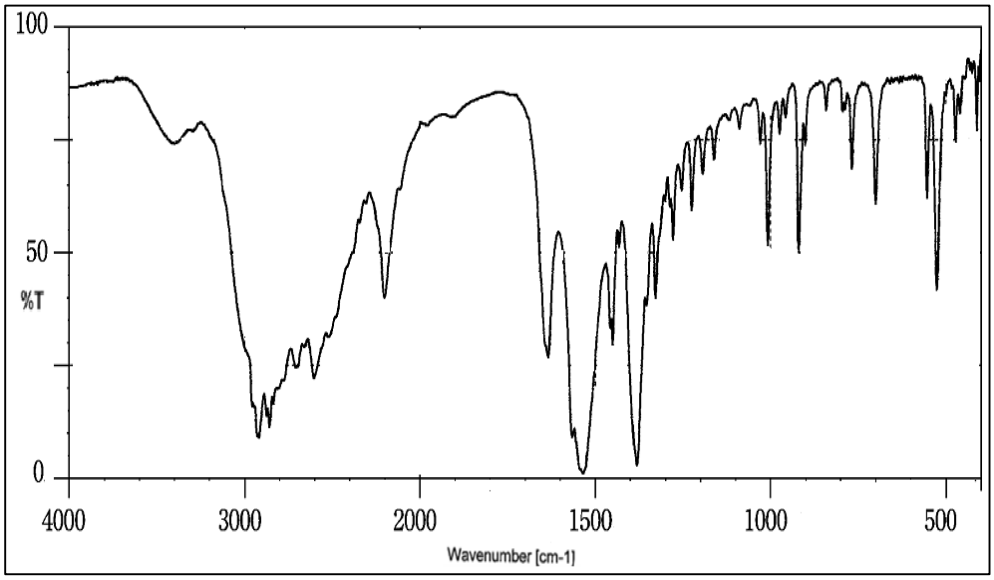

Fig 2a: Infra-red spectra for tranexamic acid

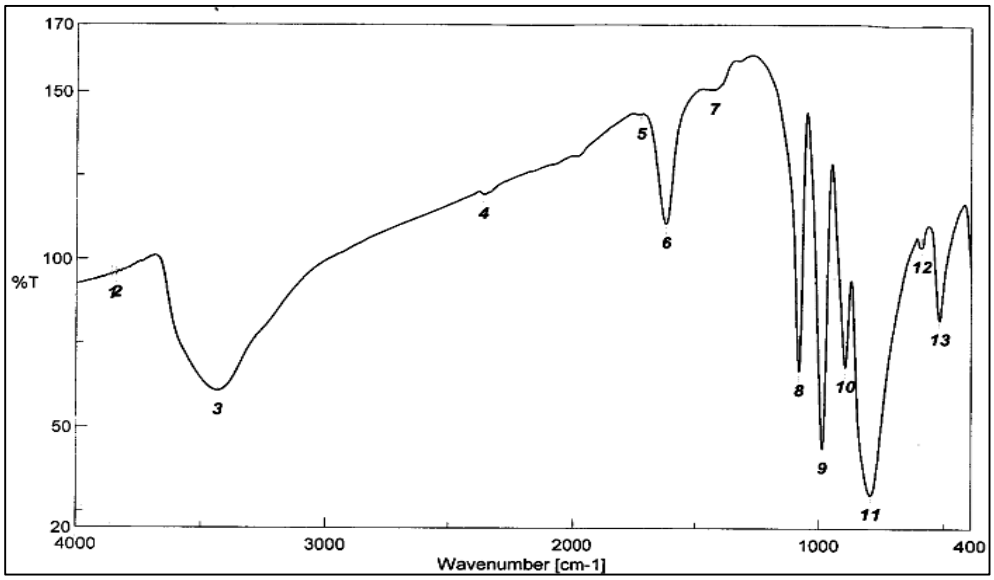

Fig 2b: Infra-red spectra for (PTA).

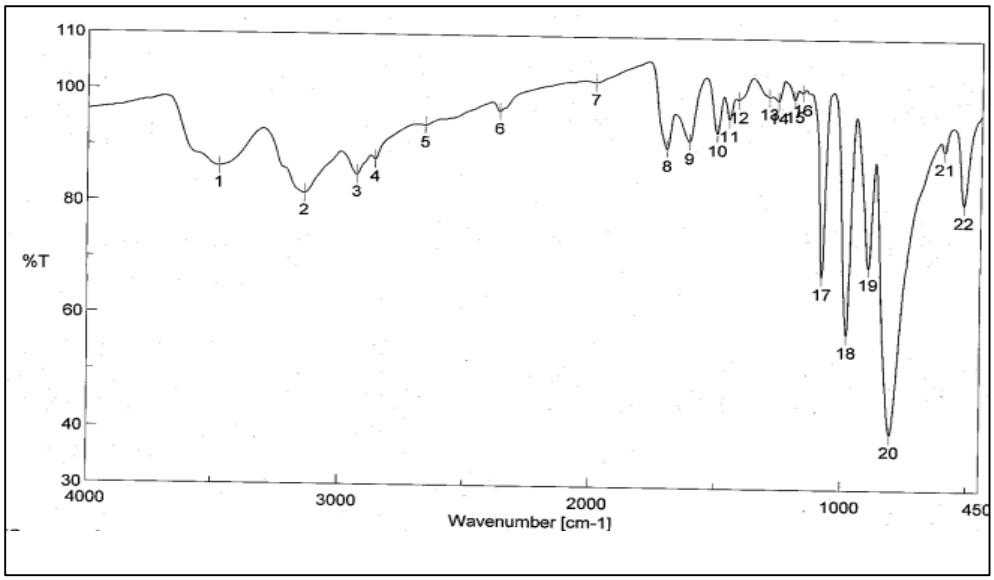

Fig 2c: Infra-red spectra for (TXA-PTA)

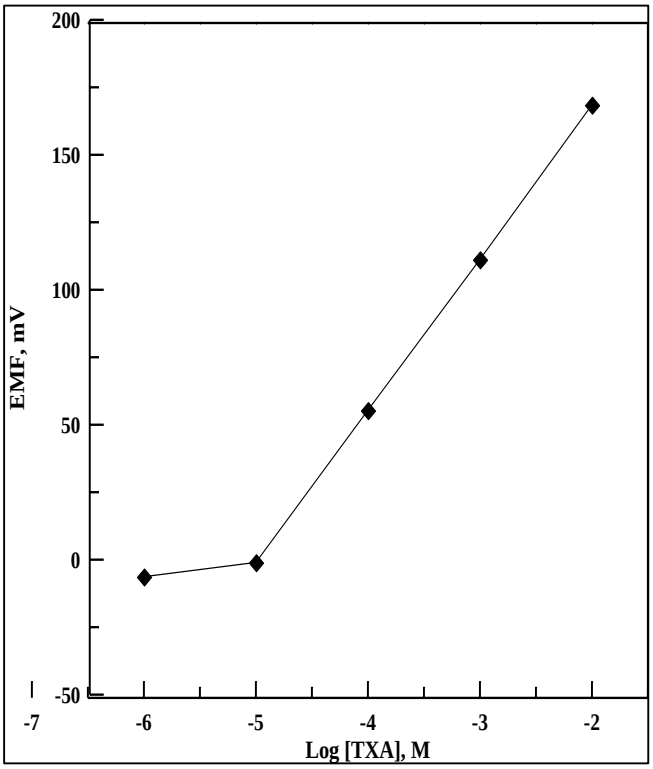

Fig 3: Calibration curve of the Tranexamic acid membrane sensor no: (7)

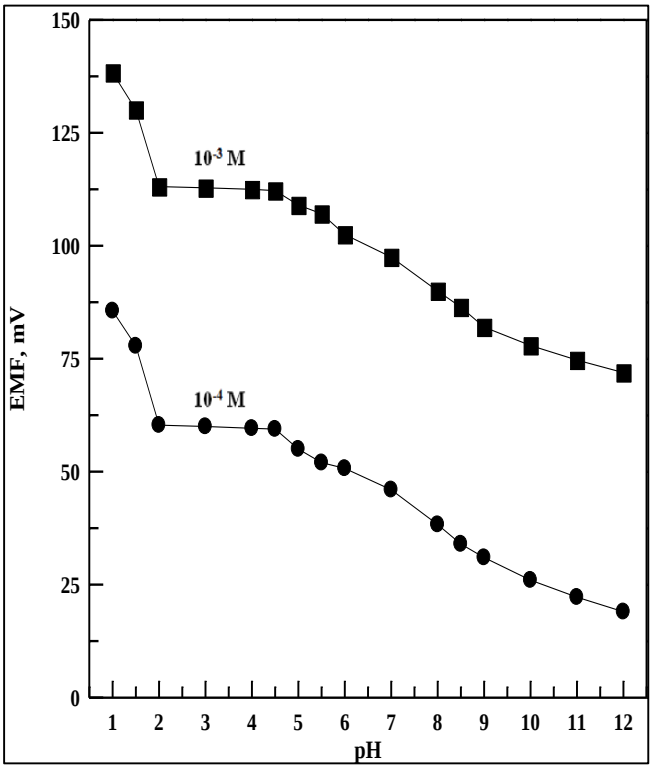

Fig 4: Effect of pH on TXA-electrode performance.

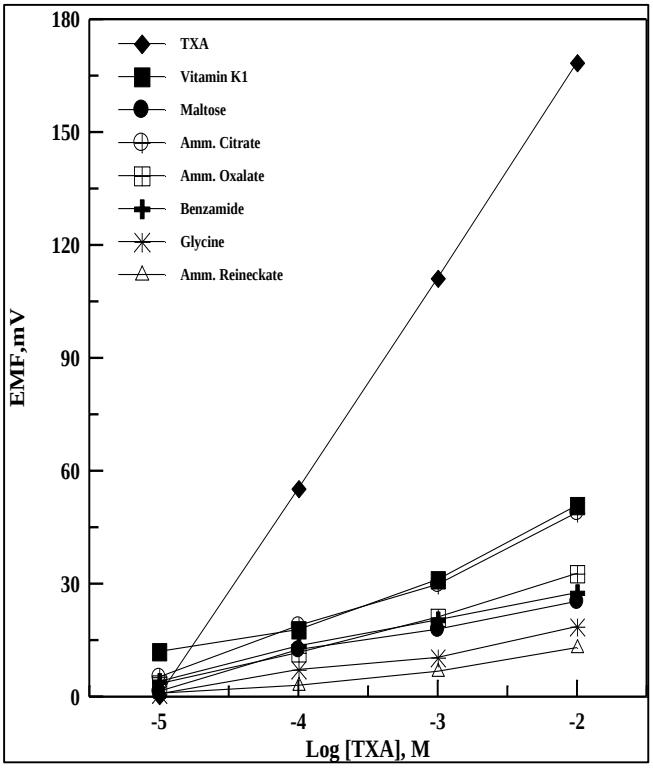

Fig 5a: Selectivity of (TXA) membrane

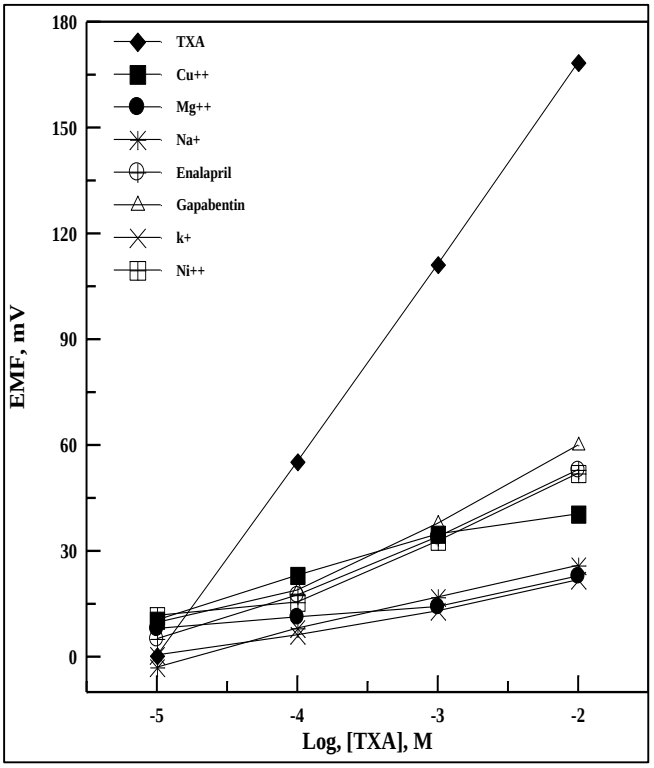

Fig 5b: Selectivity of (TXA) membrane

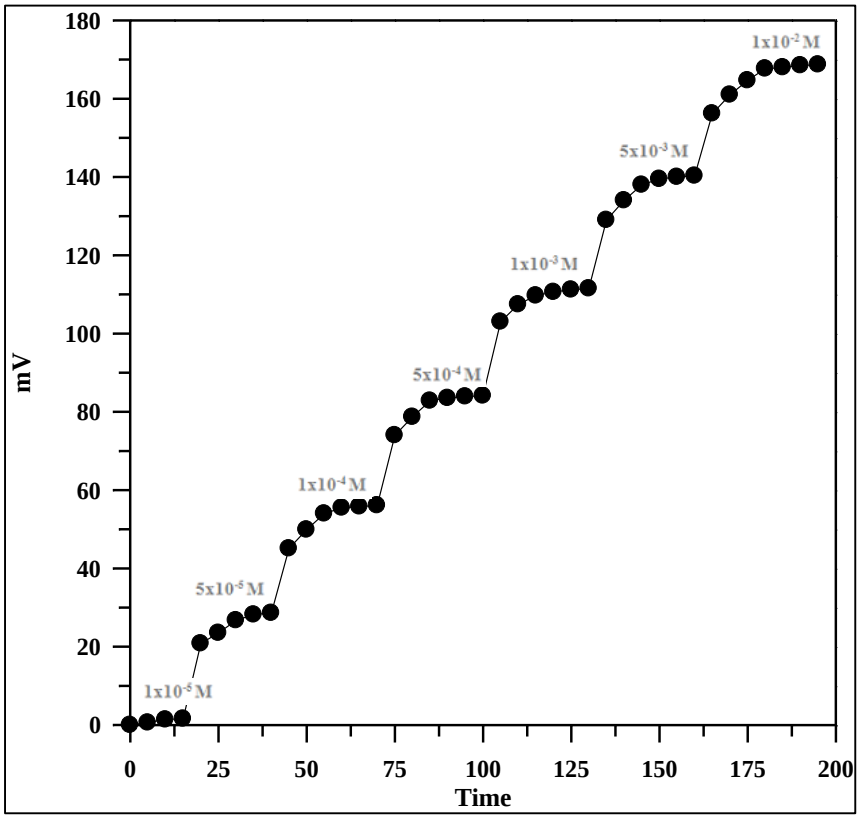

Fig 6: Dynamic response time of the TXA membrane sensor

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