New Validated Potentiometric Determination of Vasodilator Pentoxifylline in its Pharmaceutical Formulations and Biological Fluids

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The construction and performance characteristics of pentoxifylline selective electrodes were developed. Two types of electrodes: plastic membrane I and coated wire II were constructed based on the incorporation of pentoxifylline with phosphotungstic acid (PTA). The influence of membrane composition, kind of plasticizer, pH of the test solution, soaking time, and foreign ions on the electrodes was investigated. The electrodes showed a Nernstain response with a mean calibration graph slope of 56.77 ± 0.19 and 55.76 ± 0.71 mV decade^{-1} at 25 ºC for electrode I and II respectively, over pentoxifylline concentration range from 1.0×10^{-5}-1.0×10^{-2} and 9.0×10^{-6}-1.0×10^{-2} mol L^{-1}, with detection limits 4.89×10^{-6} and 3.90×10^{-6} mol L^{-1} for electrode I and II, respectively. The pH range of the constructed electrodes was 4-6. Interferences from common cations, alkaloids, sugars, amino acids and drug excipients were reported. The results obtained by the proposed electrodes were also applied successfully to the determination of the drug in its pharmaceutical preparations and biological fluids.

Keywords: Plastic membrane; Coated wire electrode; Ion-selective electrode; Pentoxifylline; Potentiometric determination; Pharmaceutical formulation; Biological fluids.

1. INTRODUCTION

Pentoxifylline, 1-(5-oxohexyl)-3,7-dimethylxanthine Fig. 1, is an active haemorheological drug widely used for the treatment of intermittent claudication and other circulatory disorders.[1] Because the drug improves perfusion in the impaired microcirculation of peripheral and cerebral vascular beds, it has also been tried as therapy for cerebrovascular disorders.[2] It is a white to creamy white, crystalline powder, soluble in water and ethanol and sparingly soluble in toluene.[3] Several methods for its determination have been reported, both in body fluids and pharmaceuticals, including high performance liquid chromatography,[4-6] liquid chromatography coupled with mass spectrometry,[7,8] spectrofluorimetry,[9] spectrophotometry,[10] high performance thin layer chromatography[11] and gas chromatography.[12] This work describes new selective membrane sensors, of two types: plastic membrane and coated wire electrodes for the determination of pentoxifylline in pure solutions, pharmaceutical preparations and biological fluids. The advantages of the electrochemical method over other reported methods are simple design, small size sensors, short measurement time, low cost, adequate precision, high accuracy, low detection limit and wide analytical range. Moreover, the method is simple, easy to operate and inexpensive making it an excellent tool for the routine determination of pentoxifylline in quality control laboratories.

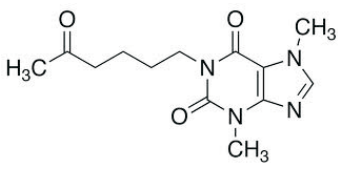

Fig. 1. Chemical structure of pentoxifylline.

2. EXPERIMENTAL

2.1. Reagents and Materials

All chemicals used were of analytical grade, pure grade pentoxifylline was kindly supplied from Sanofi Aventis Company. The pharmaceutical preparation (Trental® 400 mg/tablet) was purchased from local drug stores. Methanol 99.0%, Acetone 99.9%, *o*-nitrophenyl octyl ether (*o*-NPOE) 99.0% and tetrahydrofuran (THF) 97.0%

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were provided by Fluka, Switzerland. Polyvinyl chloride (PVC) high molecular weight and phosphotungstic acid 99.09% were provided by Sigma-Aldrich Germany. Urine samples were obtained from healthy volunteers and serum samples (Multi-Serum Normal, Ranbdox, Laboratories, UK) were obtained from commercial sources.

2.2. Instruments

The electrochemical measurements were carried out using Jenway 3040 pH-meter (UK) with an indicator electrode in conjunction with double junction Ag/AgCl (Orion 90-20) (Taiwan, R.O.C.) containing 10% w/v potassium nitrate in outer compartment. Orion pH-meter (Model 420 A) was used for pH measurements. An Orion 91-02 glass-calomel combination electrode, (Taiwan, R.O.C.) was used for pH adjustment.

2.3. Standard Drug Solution

Stock pentoxifylline solution (0.1 mol L^{-1}) was prepared daily by dissolving an appropriate amount of the drug in distilled water. Working solutions were prepared by appropriate dilution using distilled water.

2.4. Preparation of Pentoxifylline-phosphotungstate Ion-pair

The ion-pair was prepared by mixing stoichiometric amounts of 1.0×10^{-2} mol L^{-1} phosphotungstic acid with an equimolar solution of pentoxifylline and stirred for 10.0 min. The resulting white precipitate was filtered, washed thoroughly with distilled water and dried at room temperature for 24 h.

2.5. Membrane Composition

The membrane composition was studied by varying the percentages (w/w) of the ion pair, poly (vinyl chloride) PVC and plasticizer *o*-nitrophenyl octyl ether (*o*-NPOE), until the optimum composition that exhibits the best performance characteristics was obtained. The membranes were prepared by dissolving the required amount of the ion-pair, PVC and (*o*-NPOE) in 5.0 mL tetrahydrofuran (THF). The solution mixture was poured into a petri dish (3.0 cm diameter), covered with a filter paper and the solvent was allowed to evaporate slowly at room temperature. To obtain the uniform membrane thickness, the amount of THF was kept constant and its evaporation was fixed for 24 h.

2.6. Electrode Construction

Plastic membrane electrode: A punched circular membrane was attached to a poly-ethylene tube (8.0 mm diameter) in an electrode configuration by means of PVC-THF solution. A mixture containing equal volumes of 1.0×10^{-3} mol L^{-1} pentoxifylline and potassium chloride was used as internal reference solution in which the Ag/AgCl reference electrode was dipped. The constructed electrode was pre-conditioned after preparation by soaking for 8 h in 1.0×10^{-3} mol L^{-1} pentoxifylline and stored in the same solution. All potentiometric measurements were performed using the following cell assembly: Ag/AgCl/internal solution/membrane/test solution//KCl salt bridge//SCE.

Coated wire electrode: Pure aluminum wire of 4.0 cm length was tightly insulated by polyethylene tube leaving 1.0 cm at one end for the coating and 0.5 cm at the other end for connection. The coating solution was described previously under membrane composition. Prior to coating, the polished aluminum surface was washed with a detergent, thoroughly rinsed with water, and dried with acetone. Then the wire was rinsed with chloroform and allowed to dry. Afterwards, the aluminum wire was coated by quickly dipping it into the coating solution several times and allowing the film left on the wire to dry for about 3 min. The process was repeated several times until a plastic membrane of approximately 1.0 mm thickness was formed. The prepared electrode was conditioned by soaking for 6 h in 1.0×10^{-3} mol L^{-1} pentoxifylline solution. All potentiometric measurements were performed using the following cell assembly: Al/membrane/test solution//KCl salt bridge//SCE.

3. ANALYTICAL APPLICATIONS

3.1. Potentiometric Determination of Pentoxifylline

3.1.1. Pure drug

Pentoxifylline has been determined potentiometrically using the investigated electrodes in the concentration range 1.0×10^{-5}-5.0×10^{-3} and 9.0×10^{-5}-5.0×10^{-3} in direct and standard addition method for both plastic and coated wire electrodes, respectively.

3.1.2. Trental® Tablets

Ten tablets were finely powdered and accurate weight equivalent to prepare 1.0×10^{-2} mol L^{-1} was prepared using distilled water. Serial dilutions were done to obtain different concentrations in the range of 5.0×10^{-5}-1.0×10^{-2} mol L^{-1}, of pentoxifylline for both electrodes I and II. The pentoxifylline-electrode(s) was immersed in the solution. The electrode(s) system was allowed to equilibrate with stirring; the electromotive force (emf) recorded and compared with the calibration graph.

3.1.3. Content Uniformity Assay of Trental® Tablets

Ten individual tablets of Trental® (400 mg/tablet) were placed separately in 100-mL beakers and dissolved in

10.0 mL distilled water, complete to volume of distilled water. The electrode(s) was directly immersed into 10.0 mL of each sample solution for five times and then washed with distilled water to reach steady potential between the individual measurements. The mean potential was used to evaluate the content uniformity from the calibration graph.

3.2. Application to Serum and Urine

Pentoxiphylline has been determined in human urine and serum by the investigated electrodes. 5 mL of human urine or human serum was transferred into 50-mL volumetric flask and diluted to volume using distilled water. Accurate weights of pentoxifylline equivalent to the concentration range of 5.0×10^{-5}-1.0×10^{-3} and 1.0×10^{-5}-1.0×10^{-3} mol L^{-1} were added for urine and serum, respectively. The procedure under electrode calibration was applied.

4. RESULTS AND DISCUSSION

4.1. Optimization of Membrane Composition

In this study three membrane compositions were investigated, the results were summarized in Table 1. The results showed that the electrode(s) made by membrane of type (a) with 2.0 w% Pentoxifylline-phosphotungstate ion pair, 32.0 w% PVC and 66.0 w% plasticizer *o*-NPOE exhibited the best performance characteristics (slope 56.77 ± 0.19 and 55.76 ± 0.71 mV $decade^{-1}$ at 25 ºC for electrode I and II, respectively, over pentoxifylline concentration range from 1.0×10^{-5}-1.0×10^{-2} and 9.0×10^{-6}-1.0×10^{-2} mol L^{-1} for the previously mentioned electrodes, respectively.

4.2. Nature and Response Characteristics of the Electrodes

Pentoxifylline reacts with phosphotungstic acid to form a stable pentoxifylline-phosphotungstate ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran. The complex was prepared and tested as active material with *o*-NPOE as a solvent mediator in a poly (vinyl chloride) membrane response for pentoxifylline. The critical response characteristics of plastic membrane and coated wire electrodes were determined and results are summarized in Table 2. The electrode(s) exhibited a Nernstain response over the concentration ranges 1.0×10^{-5}-1.0×10^{-2} and 9.0×10^{-6}-1.0×10^{-2} mol L^{-1} pentoxifylline with slopes 56.77 ± 0.19 and

Table 1. Optimization of membrane composition (w/w %) of pentoxifylline sensors

Types	m	PVC w%	o-NPOE w%	Ion-Pair w%	Slope	RSD%	r	Linear Conc. Range
Plastic	(a)	32.0	66.0	2.0	56.77	0.1	0.9997	1.0×10^{-5}-5.0×10^{-2}
membrane	(b)	35.0	64.0	1.0	54.37	0.7	0.9994	1.0×10^{-5}-1.0×10^{-2}
electrode	(c)	36.0	60.0	4.0	51.44	1.1	0.9991	1.0×10^{-5}-1.0×10^{-2}
Coated wire	(a)	32.0	66.0	2.0	55.76	0.7	0.9999	9.0×10^{-6}-1.0×10^{-2}
electrode	(b)	35.0	64.0	1.0	53.81	0.2	0.9992	1.0×10^{-5}-1.0×10^{-2}
	(c)	36.0	60.0	4.0	48.74	0.3	0.9994	5.0×10^{-5}-1.0×10^{-2}

Table 2. Critical response characteristics of pentoxifylline-phosphotungstate sensors

Parameter[a]	Plastic membrane electrode	Coated wire electrode
Slope (mV per decade)	56.77 ± 0.19	55.76 ± 0.71
Intercept	329.39	396.24
Correlation coefficient r.	0.9997	0.9999
Linear range (mol L^{-1})	1.0×10^{-5}-1.0×10^{-2}	9.0×10^{-6}-1.0×10^{-2}
Detection limit (mol L^{-1})	4.89×10^{-6}	3.9×10^{-6}
Response time for 10^{-3} mol L^{-1} (s)	25	≤15
Working pH range	4-6	4-6
Lifetime /day	30	28
Accuracy ± SD	99.46 ± 0.5	99.37 ± 0.6
Repeatability (CV_w %)	0.6	0.8
Between day variability (CV_b %)	0.8	0.9

[a] Mean of three measurements

55.76 ± 0.71 mV decade^{-1} for electrode I and II respectively, (Fig. 2). The choice of membrane solvent to achieve the required selectivity is based on its electric permittivity and its immiscibility with aqueous phase, high viscosity, low solubility of the matrix in the membrane and ability to dissolve ion-pair complex.

4.3. Life time

The response time of the electrode(s) was tested for 1.0×10^{-1}-1.0×10^{-6} mol L^{-1} pentoxifylline solutions. The sequence of measurements was from low to high concentrations. The electrode(s) exhibited a fast and dynamic response of 25 and ≤ 15 s for a period of 28 and 35 days for electrode I and II respectively, without significant change in the electrode(s) parameters.

4.4. Effect of Plasticizer

In this study, three plasticizers, di-butylphthalate (DBP), di-octylphthalate (DOP) and *o*-nitrophenyl octyl ether (*o*-NPOE) were used to examine the optimization of the membrane. The results obtained showed that the response performances of the prepared membranes were rather different depending on the use of plasticizer, the proportion of the plasticizer toward PVC and toward the electroactive compound. The typical potential responses of the electrodes constructed with three plasticizers were given in Fig. 3. As shown in this Figure, the *o*-NPOE-PVC electrodes were superior to DBP- and DOP-PVC electrodes in both the response slope and linear concentration range. Thus *o*-NPOE was selected as the plasticizer of the membranes. The best membrane composition of the *o*-NPOE-PVC electrode(s) was 32.0 w% PVC, 66.0 w% *o*-NPOE and 2.0 w% ion-pair.

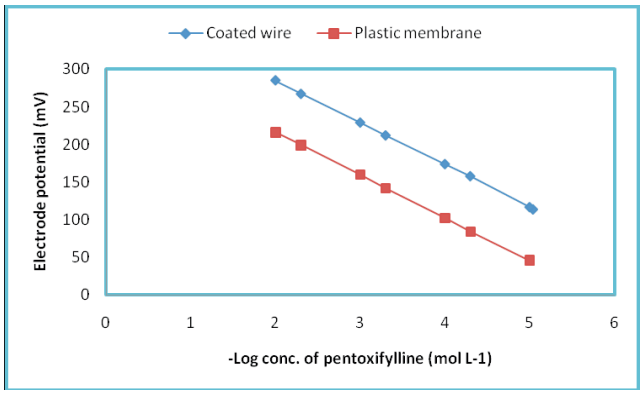

Fig. 2. Typical calibration graphs of pentoxifylline sensors.

4.5. Effect of Soaking

The performance characteristics of the pentoxifylline-phosphotungstate electrode(s) was studied as a function of soaking time. For this purpose the electrode(s) was soaked in 1.0×10^{-3} mol L^{-1} solution of pentoxifylline, the calibration graphs were plotted and the optimum soaking time was found to be 8 h and 6 h at which the slope of the calibration curve was 56.77 ± 0.19 and 55.76 ± 0.71 mV decade^{-1}, at 25 ºC for electrode I and II, respectively. The influence of prolonged soaking on the lifetime of pentoxifylline-phosphotungstate electrode(s) was followed by constructing calibration plots. The electrode(s) was soaked continuously on 1.0×10^{-3} mol L^{-1} solution of pentoxifylline for 24 h, 7, 15, 20, 28 and 30 days. The calibration plot slopes decreased slightly to 53.96 and 54.41 mV decade^{-1} after 20 and 28 days for the previously mentioned electrodes, respectively.

4.6. Regeneration of the Electrode

The above discussion revealed that soaking of the electrode(s) in the drug solution for a long time has a negative effect on the response of the membrane towards pentoxifylline. The same effect appears after working with the electrode(s) for a long time. The regeneration of the electrode(s) was tried simply by reformation of the ion-exchange on the external gel layer of membrane.[13] The regeneration of the pentoxifylline-phosphotungstate membrane was successfully achieved by soaking the exhausted electrode(s) for 24 h in a solution that was 1.0×10^{-2} mol L^{-1} phosphotungstic acid, followed by soaking for 3 h in 1.0×10^{-2} mol L^{-1} pentoxifylline solution. Fig. 4, shows the calibration graphs for the exhausted electrode and regenerated plastic membrane electrode. It was found that the lifespan of the regenerated electrode(s) is limited to 6 h due to the

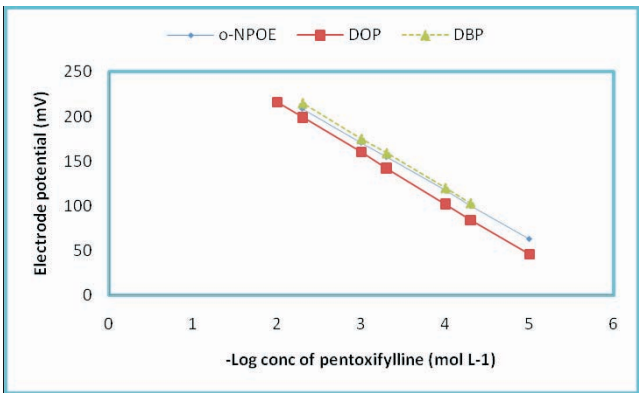

Fig. 3. Effect of plasticizers on pentoxifylline sensors.

ease of leaching of the lipophilic salts from the gel layer at the electrode(s) surface compared with those that are attached homogeneously to the PVC network through the solvent mediator.

4.7. Effect of pH

The effect of pH of the pentoxifylline solution using 1.0×10^{-3} mol L^{-1} pentoxifylline on the electrode(s) potential was investigated. The solution was acidified by the addition of very small volumes of 0.1 mol L^{-1} hydrochloric acid then the pH value was increasing gradually using 0.1 mol L^{-1} sodium hydroxide. The potential for each pH value was recorded and then the potential-pH curves for pentoxifylline concentration were constructed as shown in Fig. 5. It is obvious that the electrode(s) potential is practically independent in the pH range 4-6.

4.8. Selectivity of the Electrodes

The influence of various basic substances on the response of pentoxifylline sensors was investigated by measuring the potentiometric interference of different kinds of sugars, inorganic cations, certain alkaloids and amino acids. The selectivity coefficients were evaluated by the separate solution method. Table 3, showed that the proposed pentoxifylline-phosphotungstate membrane electrode(s) is highly selective toward pentoxifylline. The electrode(s) showed no response to a number of potentially interfering ionic excipients usually used in the manufacturing of the pharmaceutical preparations, such as starch and lactose. The inorganic cations did not interfere due to the differences in their mobilities and permiabilities as compared with pentoxifylline cation. In the case of amino acids, the high selectivity is mainly attributed to the difference in polarity and lipophilic character of their molecules relative to pentoxifylline.

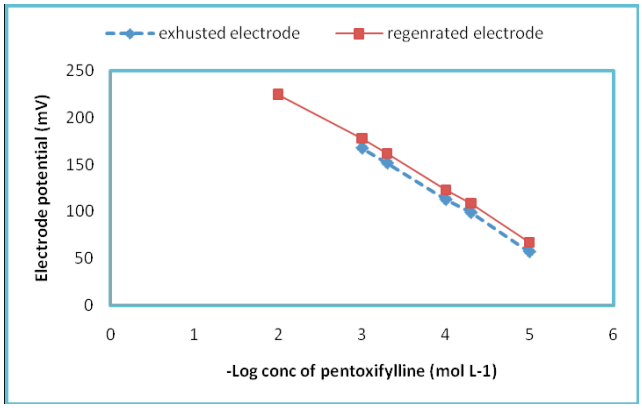

Fig. 4. Regeneration of pentoxifylline-phosphotungstate plastic membrane.

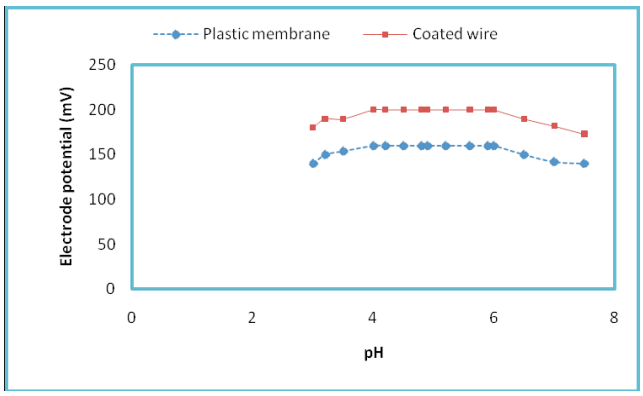

Fig. 5. Effect of pH on potential (mV) of pentoxifylline sensors using 1×10^{-3} mol L^{-1}.

4.9. Quantification of Pentoxifylline

Direct potentiometric determination of pentoxifylline using pentoxifylline-phosphotungstate electrode(s) type I and II was performed and calculated from the calibration curve. The direct potentiometric determination of pentoxifylline in pure form using the proposed electrodes gave average % recovery of 99.46 ± 0.52 and 99.37 ± 0.57 for electrode I and II, respectively. Furthermore, the results obtained were compared with those of the official method[14] (potentiometric titration using 0.1 mol L^{-1} perchloric acid, for determination of pentoxifylline) and the results are

Table 3. Selectivity coefficients and tolerance values for the pentoxifylline responsive electrodes

Interferent	Plastic membrane electrode	Coated wire electrode
Na^+	5.1×10^{-3}	7.6×10^{-3}
K^+	8.4×10^{-3}	3.4×10^{-3}
NH_4^+	6.5×10^{-3}	2.5×10^{-3}
Ca^{2+}	2.2×10^{-3}	2.1×10^{-3}
Mg^{2+}	1.3×10^{-3}	1.9×10^{-3}
Urea	7.1×10^{-3}	5.8×10^{-3}
Quinidine	3.6×10^{-3}	2.1×10^{-3}
Atropine sulphate	4.0×10^{-4}	1.7×10^{-4}
Lactose	1.1×10^{-4}	2.9×10^{-4}
Maltose	8.2×10^{-3}	7.3×10^{-4}
Glucose	9.7×10^{-3}	7.3×10^{-4}
L-leucine	4.4×10^{-3}	1.9×10^{-3}
L-Valine	7.6×10^{-4}	3.4×10^{-3}
L-Cystine	2.8×10^{-4}	1.5×10^{-3}
Starch	3.1×10^{-4}	3.4×10^{-4}
Peudoephedrine HCl	2.2×10^{-3}	6.6×10^{-3}

Table 4. Statistical treatment of the data obtained for the determination of pentoxifylline by the proposed and official method[14]

Drug form	Plastic membrane		Coated wire		Official method
	Calibration graph	Standard Addition method	Calibration graph	Standard Addition method	
Pure Form					
Mean	99.46	99.18	99.37	99.24	99.49
SD	0.52	0.63	0.57	0.39	0.38
SE	0.21	0.26	0.23	0.16	0.15
t-test	0.12 (2.228)*	1.023 (2.228)*	0.65 (2.228)*	1.33 (2.228)*	
F-test	1.89 (5.05)*	2.85 (5.05)*	1.71 (5.05)*	1.25 (5.05)*	
Trental® 400 mg/tablets					
Mean	98.79	98.84	98.89	98.69	99.38
SD	0.66	0.45	0.95	0.63	0.43
SE	0.27	0.17	0.36	0.24	0.18
t-test	1.84 (2.228)*	2.19 (2.201)*	0.52 (2.201)*	1.24 (2.201)*	
F-test	2.29 (5.05)*	1.09 (4.39)*	2.36 (4.39)*	1.02 (4.39)*	

* The Figures in parentheses are the tabulated t- and F-test at p = 0.05[17]

listed in Table 4.

5. VALIDATION OF THE PROPOSED METHOD

5.1. Accuracy

The accuracy of the proposed ion selective electrode (ISE) method was investigated by the determination of pentoxifylline in spiked placebo samples prepared from serial concentrations of pentoxifylline reference standards. The results show that the proposed method is an accurate one for the determination of pentoxifylline in its pharmaceutical preparations without interfering from the coformulated adjuvants as indicated by the percentage recovery values (99.29 ± 0.31 and 99.19 ± 0.71).

5.2. Linearity

Under the optimal experimental ISE conditions, a linear relationship exists between the electrode potential/mV and the logarithm of corresponding concentration of the investigated drug. The regression data, correlation coefficient (r) and other statistical parameters are listed in Table 2.

5.3. Detection Limit

The detection limit of the investigated drug was calculated according to IUPAC[15] recommendation which stated that the detection limit is the concentration at which the measured potential differs from that predicted by the linear regression by more than 18 mV. The values were reported in Table 2; indicate that the proposed method is sensitive for detection of very small concentrations of pentoxifylline.

5.4. Precision

The precision of the proposed method, measured as percentage relative standard deviation (RDS %) was tested by repeating the proposed method for determination of the investigated drug in its pharmaceutical preparations "three batches" to nine replicates. The RSD% values for the repeated determinations were 0.58%, 0.67% and 0.35% for determination of pentoxifylline in Trental® tablets using pentoxifylline-phosphotungstate plastic membrane electrode and 0.74%, 0.49% and 0.69% in Trental® tablets using pentoxifylline-phosphotungstate coated wire electrode. The above RSD% values are less than 2% indicating good precision.

5.5. Robustness and Ruggedness

The robustness of the proposed method was tested by investigating the capacity of the method to remain unaffected by a small but a deliberate variation in method parameters and provides an indication of its reliability during

Table 5. Determination of pentoxiphylline in spiked technique in human serum and urine using pentoxiphylline electrodes

Statistical parameters	Plastic membrane electrode		Coated wire electrode	
	Urine solution	Serum solution	Urine solution	Serum solution
Mean ± SD	98.52 ± 0.62	98.36 ± 0.44	98.99 ± 0.86	98.88 ± 0.73
n	6	6	6	6
Variance	0.38	0.19	0.73	0.53
SE	0.25	0.18	0.35	0.29
% RSD	0.63	0.45	0.86	0.73

normal usage.[16] The robustness of the proposed method was carried out by using phosphate buffer pH 6 ± 1 and the percentage recoveries were 99.92 ± 0.24 and 99.98 ± 0.27 for the two prepared I and II electrodes, respectively. These results were closely in agreement with those obtained from standard drug solutions. While the ruggedness of the proposed method was investigated by measuring the degree of reproducibility at test results obtained by the analysis of the same samples under a variety of conditions such as different laboratories, analysts and instruments. The reproducibility using another model of pH-meter (Orion pH-meter, Model 420 A) was tested and the results obtained were (99.99 ± 0.13 and 99.94 ± 0.16) for plastic and coated wire electrodes, respectively whose show that this method is reproducible.

6. ANALYTICAL APPLICATIONS OF THE PROPOSED METHOD

6.1. Application to pharmaceutical preparations

6.1.1. Trental® Tablets

The proposed ISE method was applied for determination of pentoxifylline in its dosage forms. The mean % recovery found and RSD%, indicate that the proposed validated method could be adopted for the determination of the investigated drug in its pharmaceutical preparations without interference from the coformulated adjuvants. Table 4, shows the results obtained by the proposed and official methods for the determination of pentoxifylline in pure form and in tablets.

6.1.2. Content Uniformity Assay of Trental® Tablets

The proposed ISE method described good accuracy and precision for the quality control tests, the content uniformity assay showed that the mean recoveries ± standard deviation were 99.07 ± 0.44 and 99.12 ± 0.35 for electrode I and II, respectively.

6.1.3. Application to Human Serum and Urine

The use of pentoxifylline hydrochloride drug in various clinical fields has necessitated an accurate, rapid and quantitative analysis in various matrices (dosage forms and biological fluids). This work proposed a fast, simple, easy, sensitive and straightforward potentiometric method to determine pentoxifylline in dosage forms without the need for preseparation and preconcentration or derivatization procedures. The potential of the pentoxifylline-phosphotungstate sensors showed no significant difference of response time between aqueous solution of pure drug and its solutions from pharmaceutical preparations and biological fluids. The proposed method describes good accuracy and precision for the determination of the drug in biological fluids using spiked technique. The results obtained were summarized in Table 5.

7. CONCLUSION

The pentoxifylline-selective electrodes based on pentoxifylline-phosphotungstate ion association in a PVC matrix exhibited useful analytical characteristics for the determination of pentoxifylline in pure form, pharmaceutical formulations and biological fluids. The good recoveries and low relative standard deviations obtained reflect the high accuracy and precision of the proposed method. Moreover, the method is simple, easy to operate and inexpensive making it an excellent tool for the routine determination of pentoxifylline in quality control laboratories.

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