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Construction and Evaluation of Aminophylline Ion-Selective Electrode in its Pharmaceutical Preparations and Biological Fluids

ABDALLA SHALABY*, ABDULKAREEM I. ABDULRAHEEM†,
MAGDA EL-MAAMLY and MAHA EL-TOHAMY
Department of Analytical Chemistry, Faculty of Pharmacy
Zagazig University, Zagazig, Egypt
E-mail: abdallashalaby@yahoo.com

A PVC membrane electrode of aminophylline and tungstophosphoric acid association complex was constructed. The basic electrode's performance characteristics were evaluated. The prepared electrode exhibits a Nernstain response (19.6 ± 0.2 mV/decade) over the concentration range of aminophylline 1×10^{-2}–5×10^{-6} M of solutions of pH 4-7. Common organic and inorganic cations showed negligible interference. Direct potentiometric determination of 1×10^{-2}–5×10^{-6} M aqueous aminophylline using this membrane electrode system showed an average recovery of 99.80 with mean standard deviation ± 0.919. The electrode gave a good stability reproducibility and fast response. These characteristics of the electrode enable it to be used successfully for the determination of aminophylline in pure form, pharmaceutical preparations and in biological fluids.

Key Words: Ion-selective electrode, Aminophylline determination, Pharmaceutical preparations, Potentiometry.

INTRODUCTION

Aminophylline, 1,3-dimethyl xanthine ethylene diamine (Fig. 1), is a respiratory smooth muscle relaxant. It is one of several drugs known as xanthine derivatives which are the mainstay of therapy for bronchial asthma and similar diseases. It relives of bronchial asthma and breathing difficulties associated with bronchitis and other diseases[1].

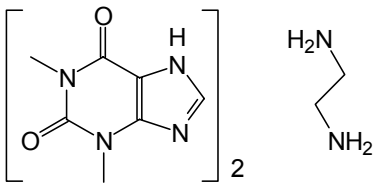

Fig. 1. Structure of aminophylline

†College of Health Sciences, Public Authority for Applied Education and Training, Kuwait.

Several methods have been reported for the determination of aminophylline including spectrophotometry[2], high performance liquid chromatography[3-7], thin layer chromatography[8], capillary zone electrophoresis[9], electrochemical methods[10], colorimetric methods[11] and chemiluminescence's methods[12]. The potentiometric methods of analysis using ion-selective electrodes are simple, economical and applicable for the samples thus, the present work describes a new selective membrane electrode of plasticized poly(vinyl chloride) type, for the determination of aminophylline in pure solutions, pharmaceutical preparations and in biological fluids. The electrode is based on the incorporation of an ion-pair complex of the tungstophosphate anion with aminophylline cation in a poly(vinyl chloride) matrix.

EXPERIMENTAL

All chemicals used of analytical or pharmacopoeial grade. Doubly distilled water was used throughout the experiments. Aminophylline was provided by Cid Co. (Egypt), poly(vinyl chloride) (PVC) was from Aldrich (Germany), dibutyl sebacate was from (Fluka, Switzerland), tungstophosphoric acid and tetrahydrofuran were from Memphis-Delagrange, (France), Cidophylline ® ampoules from (Cid Co. Egypt). Stock solution of aminophylline 10^{-1} M was prepared in deionized water. Different standard solutions (1×10^{-1}–1×10^{-6} M) were prepared by serial dilution of the stock solution. All aminophylline solutions were kept in dark at 4 ºC in airtight containers.

Jenway 3010 pH/mV meter (U.K.) with an aminophylline-PVC membrane electrode in conjunction with double junction Ag/AgCl electrode (Orion 90-02) (Taiwan, R.O.C.) containing 10 % w/v potassium nitrate in outer compartment. An Orion 91-02 glass-calomel combination electrode, (Taiwan, R.O.C.) was used for pH adjustment. All potentiometric measurements were carried out at 25 ± 1 ºC with constant magnetic stirring.

Recommended procedures

Preparation of aminophylline-tungstophosphate ion-pair: The ion-pair was prepared by mixing 50 mL aliquots of 1×10^{-2} M aminophylline and 50 mL of 1×10^{-2} M tungstophosphoric acid. The resulting white precipitate was filtered through G_4 sintered glass crucible and washed thoroughly with deionized water then dried at room temperature for 24 h.

Membrane composition: The membrane was prepared by dissolving 190 mg of powdered PVC, 0.35 mL of the plasticized (dibutyl sebacate) and 10 mg of the ion-pair in 5 mL tetrahydrofuran (THF). The solution was poured into a petri dish (3 cm in diameter), covered with a filter paper and the solvent was allowed to evaporate slowly at room temperature.

Electrode construction: A punched circular membrane was attached to a poly-ethylene tube (8 mm in diameter) in an electrode configuration by means of PVC-THF solution. A mixture containing equal volumes of 1×10^{-3} M aminophylline 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 at least 24 h in 1×10^{-3} M drug solution and stored in the same solution. The electrochemical system is represented as follow: Ag/AgCl/ inner solution/membrane/test solution//KCl salt bridge//SCE.

Electrode calibration: 10 mL aliquots of 1×10^{-1}–1×10^{-6} M standard aminophylline solutions were transferred into 50 mL beaker and the sensor in conjunction with Ag/AgCl reference electrode were immersed in the solution. The electrode was washed with deionized water and dried with tissue paper between measurements.

Effect of pH: The effect of pH on the potential of the electrode was studied using two pH/mV meters. The combined glass calomel electrode was connected to one instrument and the PVC aminophylline membrane with the double junction Ag/AgCl reference electrode was connected to the second instrument. 30 mL aliquots of 1×10^{-5} M, 1×10^{-4} M, 1×10^{-3} M and 1×10^{-2} M drug solutions were transferred to a 100 mL beaker where the three electrodes were immersed; the potential readings corresponding to different pH values were recorded. The pH was gradually increased or decreased by the addition of small aliquots of dilute solutions of (0.1 or 1.0 M) sodium hydroxide or 0.1 N hydrochloric acid respectively and the pH-mV was plotted.

Selectivity of the electrode: Selectivity coefficients were determined by the separate solution method[13], in which the following equation was applied.

$$\log K^{pot}_{Am,J^{Z+}} = (E_2 - E_1)/S + \log[AM] - \log[J^{Z+}]^{1/z}$$

where, E_1 is the electrode potential in 1×10^{-3} M aminophylline solution. E_2 is the potential of the electrode in 1×10^{-3} M solution of the interferent ion J^{z+} and the S is the slope of the calibration plot. The selectivity of the electrode towards sugars, amino acids and certain cations was studied.

Standard addition method: An electrode was immersed into a sample of 50 mL with unknown concentration (*ca.* 10^{-4} M) and the equilibrium potential of E_1 was recorded. Then 0.1 mL of 10^{-1} mL of aminophylline standard was added into the testing solution and equilibrium potential of E_2 was obtained from the change of ΔE (E_2-E_1) one can determine the concentration of the testing sample[14].

Analytical applications

Determination of aminophylline in dosage forms:

Ampoules: The prepared solution was diluted with deionized water to give different concentrations ranging from 1×10^{-6}–1×10^{-2} M. These solutions were transferred into 50 mL beaker, adjusted to pH 5 using 0.1 N dilute hydrochloric acid. The PVC-aminophylline-tungstophosphate membrane electrode was immersed in the solution. The electrode system was allowed to equilibrate with stirring and the e.m.f. was recorded and compared with the calibration graph. The standard addition (spiking technique) was also applied by recording the electrode potential after the addition of 0.1 mL of standard 1×10^{-1} M aminophylline solution to the above drug test solutions.

Content uniformity assay of cidophylline ampoules: 10 Individual ampoules were placed in separate 100 mL beaker and diluted in 90-100 mL of distilled water. Concentration of the solutions was determined by addition method as previously described.

Determination of aminophylline in biological fluids

Application to serum and urine[15]: Adjust urine pH to 5 (using 0.1 N hydrochloric acid) and pH of serum to 6 (use phosphate buffer). Add hydrochloric acid to urine and phosphate buffer to serum dropwise until the suitable pH obtained. Transfer 5 mL previously adjusted urine or serum into small separatory funnels and then add 5 mL 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5} and 10^{-6} M standard drug solution, followed by the addition of 20 mL toluene for urine or 20 mL diethyl ether for serum. Shake each funnel for 5 min and transfer aqueous layer to centrifuge tube. Centrifuge for 2 min at 1500 rpm, transfer each solution to a 50 mL volumetric flask and dilute to volume with deionized water. Apply above procedure as described under electrode calibration.

RESULTS AND DISCUSSION

Nature and response characteristics of the electrode: Aminophylline reacts with tungstophosphoric acid to form a stable ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran. The complex was prepared and tested as an active material with dibutyl sebacate as a solvent mediator in a poly(vinyl chloride) membrane response for aminophylline. The critical response characteristics of aminophylline-tungstophosphate-PVC membrane electrode were determined and results are summarized in (Table-1). The electrode exhibits a Nernstain response over the concentration range from 5×10^{-6}–1×10^{-2} M aminophylline with a cationic slope of 19.6 ± 0.2 mV/decade change in concentration as shown in (Fig. 2). The choice of membrane solvent to

TABLE-1
CRITICAL RESPONSE CHARACTERISTICS OF AMINOPHYLLINE-TUNGSTOPHOSPHATE-PVC MEMBRANE ELECTRODE

Parameter	Value
Slope (mV decade)	19.6 ± 0.2
Intercept (mV)	260.8
Linear range (M)	1×10^{-2}–5×10^{-6}
Working pH range	4-7
Response time (10-3 M) aminophylline(s)	15-20
Life time (d)	90

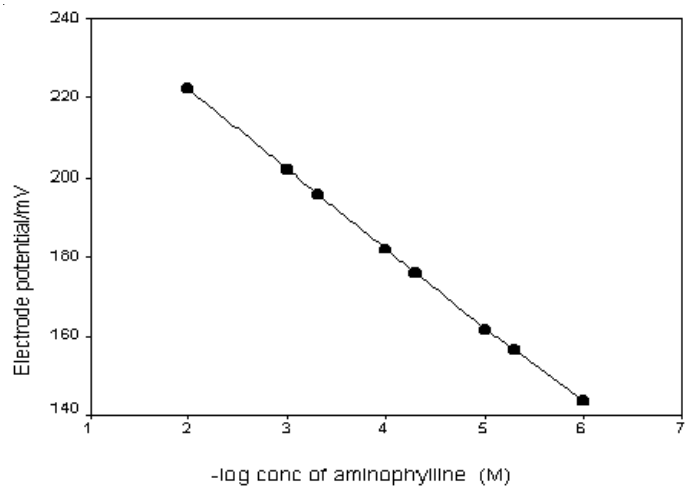

Fig. 2. Typical calibration graph of aminophylline-tungstophosphate-PVC membrane electrode

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 its ability to dissolve ion-pair complex. The response time of the electrode was tested for 1×10^{-1}–1×10^{-6} M aminophylline solutions. The sequence of measurements was from low to high concentrations. This electrode exhibits a fast dynamic response of about 20 s. The electrode was used for a period of 90 d without significant change in the electrode parameters.

Effect of pH: The effect of pH of the aminophylline solutions (10^{-5}, 10^{-4}, 10^{-3} and 10^{-2} M aminophylline) on the electrode potential was investigated. The solutions were acidified by the addition of small volumes of 0.1 N HCl acid then the pH value was increased gradually using NaOH (0.1 or 1.0 M) for each pH value, the potential was recorded and thus the

potential-pH curves for four aminophylline concentrations were constructed as shown in Fig. 3. As is obvious, within the pH range 4-7 the electrode potential is practically independent of pH and in this range the electrode can be safely used for aminophylline determination.

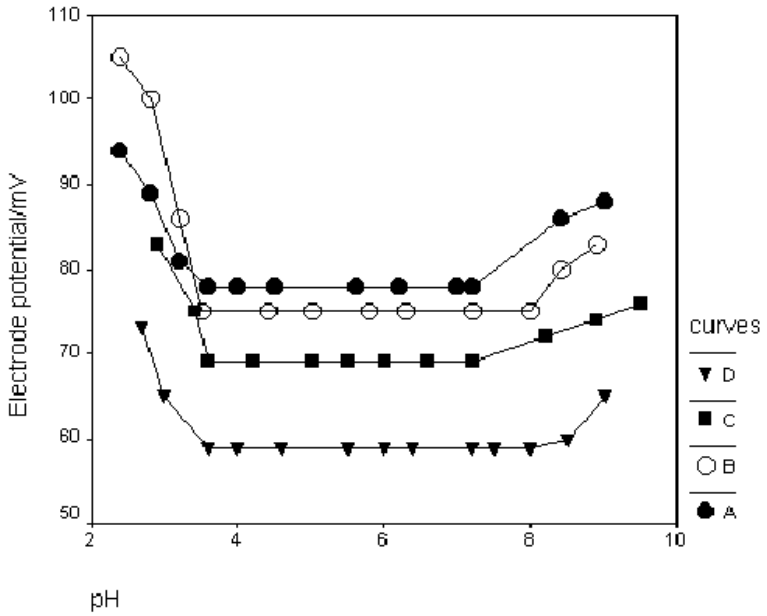

Fig. 3. Effect of pH on potential/mV of aminophylline-tungstophosphate-PVC membrane electrode, 1×10^{-2} M (A); 1×10^{-3} M (B); 1×10^{-4} M (C); 1×10^{-5} M (D)

Selectivity of the electrode: The selectivity of the ion-pair associates based membrane electrodes depends on the selectivity of the ion-exchange process at the membrane-test solution interface and the mobilities of the respective ions within the membrane. The data presented in (Table-2), showed that the proposed aminophylline-tungstophosphate-PVC membrane is highly selective toward aminophylline. The inorganic cations did not interfere due to the differences in their mobilities and permeabilities as compared with aminophylline. In the case of sugars and the high selectivity is mainly attributed to the difference in polarity and lipophilic character of their molecules relative to aminophylline.

Quantification, accuracy and precision: Direct potentiometric determination of aminophylline using the aminophylline-tungstophosphate-PVC membrane electrode was performed and calculated from the calibration curve. The statistical data of the analytical results obtained by the proposed method and official method[16] (to volume containing 0.1 g of

TABLE-2
SELECTIVITY COEFFICIENTS FOR SOME COMMON CATIONS WITH AMINOPHYLLINE-TUNGSTOPHOSPHATE-PVC MEMBRANE ELECTRODE

Interferent	$K^{Pot}_{AM^+}$	Interferent	$K^{Pot}_{AM^+}$
Glucose	4.4×10^{-3}	Magnesium sulphate	3.8×10^{-4}
Lactose	6.3×10^{-3}	Zinc sulphate	3.9×10^{-3}
Sucrose	5.6×10^{-3}	L-Valine	2.6×10^{-4}
Ammonium chloride	7.1×10^{-3}	Tryptophan	2.5×10^{-3}
Calcium chloride	3.5×10^{-3}	Atropine sulphate	1.9×10^{-3}
Potassium chloride	2.6×10^{-4}	Quinidine	1.5×10^{-3}
Sodium chloride	9.7×10^{-4}	Urea	2.8×10^{-3}
Barium chloride	2.5×10^{-3}	Sulfathiazole	1.3×10^{-3}
Nickel chloride	1.3×10^{-3}	Caffeine	2.4×10^{-3}
Sodium citrate	3.9×10^{-3}	–	–

aminophylline add sufficient 0.01 M NaOH and measure the absorbance of the resulting solution at the maximum at 275 nm) for the tested drug in pure form has been illustrated in Table-3. Furthermore, the results obtained were encouraging to apply the proposed method for the determination of aminophylline in some pharmaceutical preparations, the results obtained were compared with the official method and are listed in Table-4.

TABLE-3
DETERMINATION OF AMINOPHYLLINE IN PURE FORM USING AMINOPHYLLINE-TUNGSTOPHOSPHATE-PVC MEMBRANE ELECTRODE IN COMPARISON WITH REFERENCE METHOD[16]

Statistical parameters	Official method[16]	Direct potentiometry	
		Calibration graph	Standard addition method
Mean % recovery	99.43	99.80	99.54
N	7	8	7
Variance	0.617	0.845	0.914
SD	0.786	0.919	0.956
SE	0.297	0.325	0.361
RSD	0.790	0.921	0.960
t		(0.840)(2.160)*	(0.235)(2.179)*
F		(1.37)(3.87)*	(1.48)(4.28)*

*Theoretical values of 't' and F at p = 0.05.

From the analytical data shown in Tables 3 and 4, it is obvious that both methods (proposed and official) are in good agreement, however, the electrode method offers several advantages in term of simplicity, selectivity,

TABLE-4
COMPARATIVE ANALYTICAL RESULTS OF THE PROPOSED AND OFFICIAL METHOD FOR THE TESTED DRUG IN CIDOPHYLLINE AMPOULES

Statistical parameters	Official method[16]	Direct potentiometry	
		Calibration graph	Standard addition method
Mean % recovery	99.57	99.22	99.12
N	7	8	7
Variance	0.580	0.258	0.365
SD	0.762	0.508	0.604
SE	0.288	0.180	0.228
RSD	0.765	0.512	0.609
t		(1.031)(2.160)*	(1.225)(2.179)*
F		(2.25)(3.87)*	(1.59)(4.28)*

*Theoretical values of 't' and F at p = 0.05.

less time consuming and precision. When the investigated method was applied to biological fluids, the pH was adjusted to 5 using 0.1 N HCl and 6 for serum toluene and diethyl ether were added, respectively, for deproteination. Tables 5 and 6 show the results obtained for the determination of aminophylline in spiked human urine and serum. Thus it is recommended for the precise direct potentiometric assay of aminophylline in

TABLE-5
DETERMINATION OF AMINOPHYLLINE IN PURE FORM 'SPIKING TECHNIQUE' IN HUMAN URINE USING AMINOPHYLLINE-TUNGSTOPHOSPHATE-PVC MEMBRANE ELECTRODE

Calibration method			Standard addition method		
Taken (M)	Found [-log conc.] (M)	Recovery* (%)	Added (M)	Found [-log conc.] (M)	Recovery* (%)
5.0×10^{-6}	5.31	100.17	5.0×10^{-6}	5.29	99.79
9.0×10^{-6}	4.99	98.90	9.0×10^{-6}	5.00	99.09
1.0×10^{-5}	4.96	99.20	1.0×10^{-5}	4.98	99.60
5.0×10^{-5}	4.26	99.05	5.0×10^{-5}	4.29	99.74
9.0×10^{-5}	4.00	98.87	9.0×10^{-5}	4.01	99.12
Mean ± SD (p = 0.05)	99.24 ± 0.537			99.47 ± 0.339	
N	5			5	
Variance	0.288			0.115	
SD	0.537			0.339	
SE	0.129			0.152	
RSD	0.541			0.341	

*Average of three experiments.

TABLE-6
DETERMINATION OF AMINOPHYLLINE IN PURE FORM 'SPIKING TECHNIQUE' IN HUMAN SERUM USING AMINOPHYLLINE-TUNGSTOPHOSPHATE-PVC MEMBRANE ELECTRODE

Calibration method			Standard addition method		
Taken (M)	Found [-log conc.] (M)	Recovery* (%)	Added (M)	Found [-log conc.] (M)	Recovery* (%)
5.0×10^{-6}	5.28	99.60	5.0×10^{-6}	5.26	99.23
9.0×10^{-6}	5.00	99.09	9.0×10^{-6}	5.01	99.29
1.0×10^{-5}	4.96	99.20	1.0×10^{-5}	4.98	99.60
5.0×10^{-5}	4.24	98.58	5.0×10^{-5}	4.28	99.51
9.0×10^{-5}	4.00	98.87	9.0×10^{-5}	4.02	99.36
Mean ± SD (p = 0.05)	99.07 ± 0.380			99.40 ± 0.154	
N	5			5	
Variance	0.144			0.024	
SD	0.380			0.154	
SE	0.170			0.069	
RSD	0.384			0.155	

*Average of three experiments.

pure form, pharmaceutical preparations and biological fluids without prior separation. The content uniformity assay showed good accuracy (RSD < 1 %), with mean standard deviation ± 0.529 which give the method good agreement in laboratory assay of this drug.

Conclusion

The aminophylline selective plastic membrane electrode based on aminophylline-tungstophosphate ion association in a PVC matrix exhibited useful analytical characteristics for the determination of aminophylline in pure form, pharmaceutical preparations and biological fluids. Developed ion-selective electrode has shown good performance characteristics with time stability up to three months. This electrode is sensitive and accurate to be a privilege for applications in aminophylline determination and its quality control tests.

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