Life Science Informatics Publications
Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences
Journal Home page http://www.rjlbpcs.com/
RJLBPCS
ISSN 2454-6348

Original Research Article **DOI - 10.26479/2017.0302.14**

SYNTHESIS AND APPLICATION OF TRIMETHOPRIM SELECTIVE ELECTRODES

Amina M. Abass, Ahmed Ahmed

Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq.

ABSTRACT: This research establishes a comparative study stuck between three constructed liquid electrodes for influence trimethoprim(TMP) using direct potentiometric in various pharmaceutical preparations. TMP selective electrodes were depended on ion-pair: Trimethoprim-Molybdophsophoric acid in PVC matrix membrane with plasticizers, di-butyl phthalate(DBPH), *o*-nitro phenyl octyl ether(*o*-NPOE), tri-butyl phosphate(TBP). Electrodes were gave slopes (58.61,58.41,15.30 mV/decade), respectively, with linear ranges were about(1.2×10^{-5}-1.0×10^{-2},6.1×10^{-5}-1.0×10^{-2} and 2.5×10^{-5}-1.0×10^{-2} M), respectively. Lifetime was (45,1,2 days), respectively. The best limit of detection was 2.5×10^{-6}M for trimethoprim membrane based on DBPH. Also were studied selectivity coefficient, and PH effect.

KEYWORDS: Trimethoprim, liquid selective sensors, Trimethoprim determination.

***Corresponding Author: Dr. Ahmed Ahmed** Ph.D. * Email Address: asab1977@yahoo.com

Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq.

1.INTRODUCTION:

Trimethoprim is 5-(3, 4, 5-trimethoxybenzyl) pyrimidin-2,4-diyldiamine [1], is locked formula $C_{14}H_{18}N_4O_3$ with molecular weight 290.3 g/mol showed in Figure 1. Yellowish and white and crystallized powder or white colored crystal. Another names, Monotrim, Proloprim, 5-(3,4,5-) Trimethoxtbenzyle, Trimexazole and Trimpex. It is extensively used as an antimicrobial agent, being active versus together gram-negative and gram-positive organism [2].

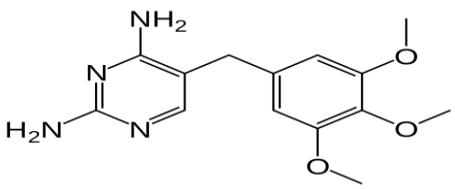


Figure 1. Structural formula of Trimethoprim.

A number of techniques have been described to determination of trimethoprim(TMP), containing method with spectrophotometry gave detection limit equal to 0.23μ mol L^{-1} in aqueous media with rang of wavelength 220-320 nm [3]. A high performance liquid chromatography analysis with flow rate near to 1 ml/min, r^2= 0.990 [4]. At wavelength 275 nm, RP-HPLC method described average retention time for trimethoprim(TMP) was found equal to 6.4 min, with linearity near to 28-52 μg/ml with (75:15:10) of solvents:KH_2PO_4(0.05 M), Acetonitrile, Methanol, respectively [5]. Spectrometry has been explained by dissolving TMP in chloroform and acetone at values of absorbance 1126 cm^{-1} [6], and by reaction between TMP with chloranilic and 2,3-dichloro-5-6-dicyano-*p*-benzoquinone, these complexes were adsorbed in 585 and 512 nm, respectively [7]. New derivative method for determination TMP at 247.8 nm [8]. Several mononuclear La(III), Cu(II), Pb(II), Zn(II), Fe(III), Co(II), Mn(II) complexes were prepared. These complexes were synthesized with mole ratio was M:DPTMEBPP =1:1, and were studied Mass XRD, NMR, thermal analysis, IR, UV-Visible for these complexes [9].

2. MATERIALS AND METHODS

Experimental Instruments

1-PH- meter, made in Romania, HANA Instruments, PH 2110.

2-(Gallen Kamp,USA) electrode of Saturated Calomel.

3-Electrode Ag /AgCl was filled with 0.1M of trimethoprim standard solution which was use up as an inner solution.

Chemicals and solutions

1-Trimethoprim standard was equipped from (Samara IRAQ-SDI) the State Company of Medical Appliances and Drug Industries.

2-Trimethoprim tablets (500 mg) from company Wadi-Al–Rafeedain(Samara-Iraq),Trimol tablets(500mg) produced by Julphar, Gulf Pharmaceutical Industries, Rass Al Kkaimah, U.A.E., Trimoks tablets (1 mg) made in Turkey were bought locally.

3- Tri-*n*-butyl phosphate 97% (TBP), *o*-nitro phenyl octyl ether 98%(ONPOE), di-*n*-butyl phthalate 99% (DBPH) were found from Switzerland, Fluka AG.

4-Stock solutions of 0.1 M for each of AlCl3, FeCl3,CaCl2, MgCl2, KCl and LiCl.

were prepared. Supplementary thinned solutions prepared by following dilution of the stockpile solutions.

Procedure

Preparation of ion-pair compound

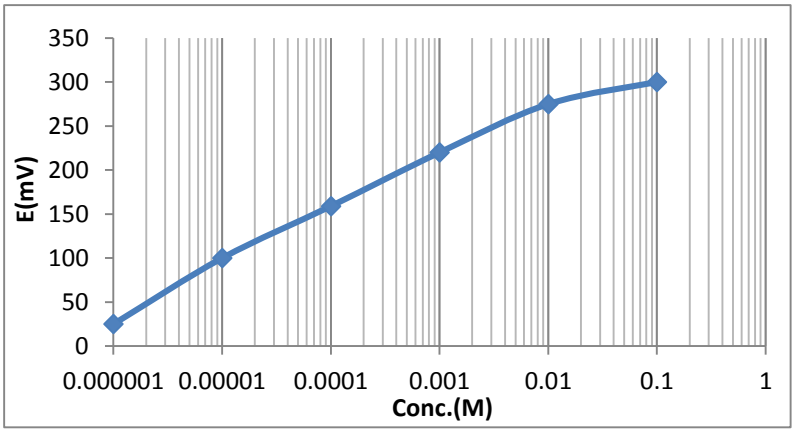
To prepared ion pair: trimethoprim(TMP)–molybdophosphoric acid (MP), were admixing 50 ml of 0.01 M molybdophosphoric acid with 50 ml of 0.01 M trimethoprim through stir up,the product precipitate was clarified, wash away with water and was dry up at 60 °C.

Assembly of ion-selective electrodes

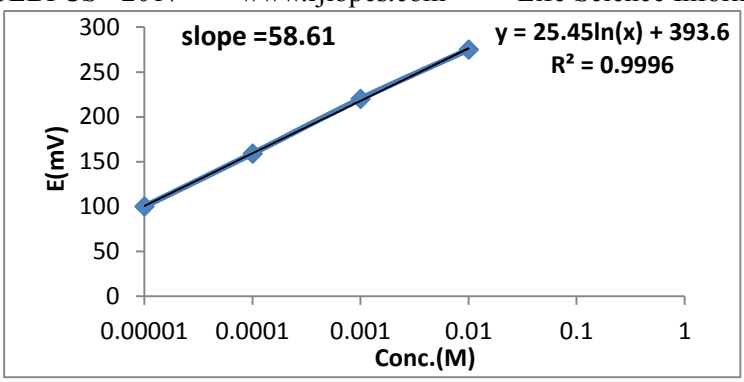
In a glass Petri dish (5 cm diameter), PVC- membrane was equipped by mingling 0.04 gm of ion exchanger complex with 0.17 gm of PVC and 0.40 gm of plasticizers and 7 ml of THF was add up. The Petri dish was cover up with a filter paper and permitted to stand for the night to allow vaporization of the solvent at room temperature [10,11], where was obtained a master membrane of 0.1 mm in thickness. A disk of 5mm diameter was cut from stock membrane, using THF to pasted the disk an exchangeable PVC tip which clipped to the bottom side of body for electrode glass.

3. RESULTS AND DISCUSSION

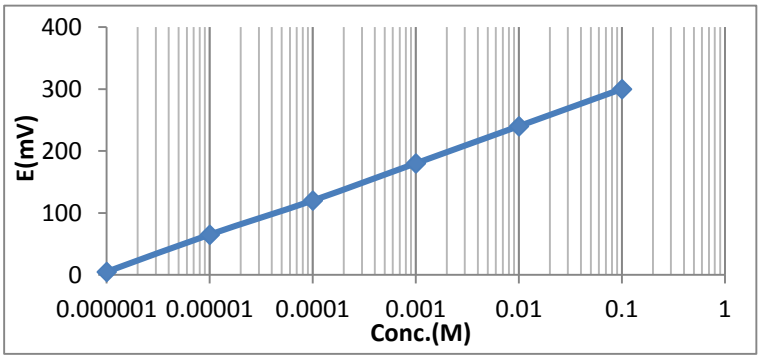
Trimethoprim-molybdophosphoric acid complex readily was soluble in tetrahydrofuran as an organic solvent. Ion pair was incorporated with PVC in membrane with the succeeding plasticizers: di-*n*-butyl phthalate (membrane A), *o*-nitro phenyl octyl ether (membrane B) and tri-*n*-butyl phosphate (membrane C).physical characteristics of trimethoprim membranes were transparent, flexible, clear there is non- Nernstain value of slope for electrode (C)(TMP+MP+TBP) was equal to15.30 mV/decade might be ascribed to low viscosity equal to (3.11 cSt) for TBP plasticizer which was lead to leakage of ion pair complex from the membrane or because the steric effect by groups of methyl [12]. Good- Nernstain slope were gave by electrode (A) (TMP+MP+BBPH) and electrode (B)(TMP+MP+NPOE) near to 58.61,58.41 mV/decade, respectively, with linear ranges were about 1.2×10^{-5}-1.0×10^{-2} and 6.1×10^{-5} -1.0×10^{-2}M, respectively.Correlation coefficient were equal to 0.9996 for both electrodes A and B. Detection limit were about 2.5×10^{-6},6.3×10^{-6}M, respectively Lifetime was close to 45 days for electrode (A) (TMP+MP+BBPH) and short time equal to 1 day for electrode (B)(TMP+MP+NPOE), this was because incompatibility of (NPOE) plasticizer with ion pair complex in matrix of PVC, or may be because type of plasticizer, NPOE which have been low viscosity near to (11.44 cSt). Response and calibration of electrodes A, B shown in graph 1, 2, 3, 4 and listed in Table 1.



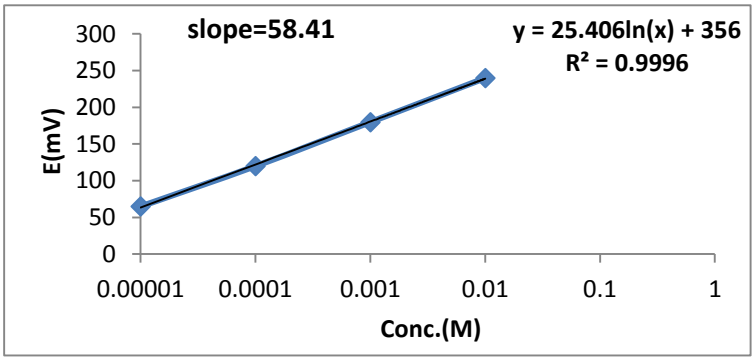
Graph 1: Response of electrode (A)(TMP+MP+DBPH).



Graph 2: Calibration curvature of electrode (A)(TMP+MP+DBPH).



Graph 3: Response of electrode (B)(TMP+MP+NPOE).



Graph 4: Calibration curvature of electrode (B)(TMP+MP+NPOE).

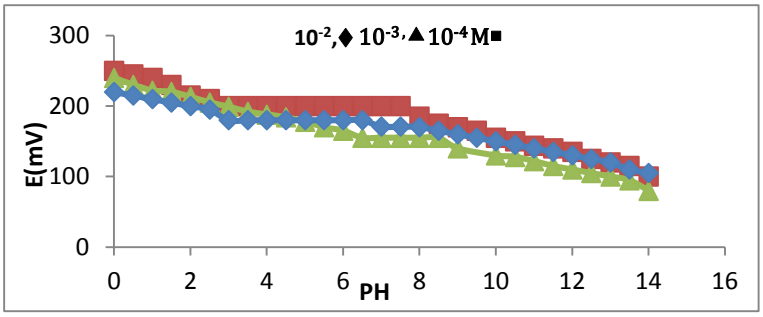
Table.1 Response of Trimethoprim electrodes (TMP-MP) .

Type.of membrane	*TMP+ MP+DBPH*	*TMP+ MP+NPOE*	*TMP+MP+TBP*
Linear range/M	1.2×10^{-5}-1.0×10^{-2}	6.1×10^{-5} -1.0×10^{-2}	2.5×10^{-5}- 1.0×10^{-2}
Correlation coefficient(R)	0.9996	0.9996	0.9997
Detection limit/M	2.5×10^{-6}	6.3×10^{-6}	5.9×10^{-6}
Slope mV/decade	58.61	58.41	15.30
Lifetime /day	45	1	2

pH Influence

Effect of pH of trimethoprim electrodes was studied by measure potential values by addition drops of 0.1 M NaOH and 0.1 M HCl to the solutions of the drugs [13], and recorded values of potentials. The achieved results are shown in typical scheme of electrode potential vs PH for electrode A at (10^{-2},$10^{-3}$and 10^{-4} M) concentration in graph 5 and Table 2 shown the range of PH for trimethoprim

electrodes. The significant potential changes at pH greater than 8.5 or less than 3.0 may ascribed to the harm of the trimethoprim membrane and variation the form of the drug at low or high function of acidic.



Graph 5:PH response of Electrode (TMP+MP+DBPH)) at three concentrations for trimethoprim solutions.

Table2: Range of PH for trimethoprim electrodes at concentration 10^{-3}M of trimethoprim solution.

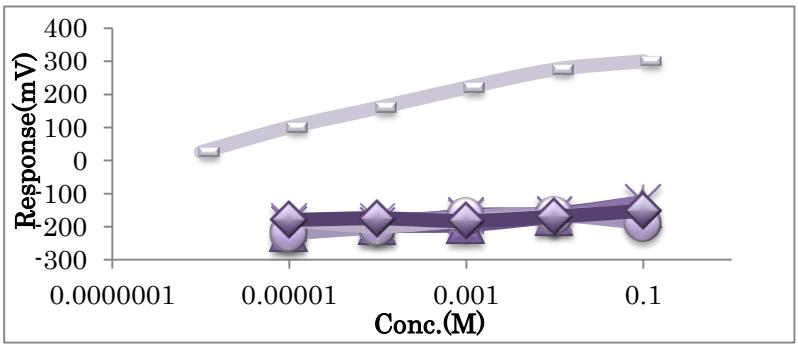
Electrode's Type	*pH range*
DBPH+MP+TMP	**3.0-8.0**
NPOE+MP+TMP	**3.0-6.5**
TBP+MP+TMP	**7.0-8.5**

Selectivity

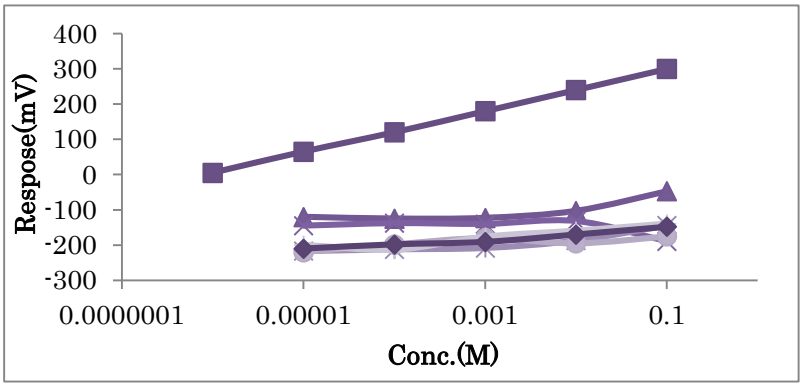
Separate solution method (SSM) was used to determined selectivity coefficient by measured potential of the electrode for both two solution: one comprising the interfering species (B) with charge ZB when (Aa=aB) and the other one comprising trimethoprim (A) with activity Aa and charge ZA(wihout B), selectivity coefficients were calculated using equation [14,15]:

$$Log.\ K_{pot}^{A,B} = [\ (EB - EA)\ z\ A\ F / 2.303\ RT\ ] + (1 - z\ A / z\ B\ )\ log\ a\ A$$

Selectivity of electrode (A) and electrode (B) for cations interferings shown in graph 6, 7 and the results were recorded in Table 3.



Graph :6 Selectivity of electrode (A)(TMP+MP+DBPH) for cations interferings.



Graph:7 Selectivity of electrode (B)(TMP+MP+NPOE)for cations interferings.

Table 3: Separate solution method for determination Selectivity Coefficient of Trimethoprim.

Electrode A(TMP+MP+DBPH)					*Electrode B(TMP+MP+NPOE)*			
Trimethoprim Concentration								
Ion	**10^{-5}**	**10^{-4}**	**10^{-3}**	**10^{-2}**	**10^{-5}**	**10^{-4}**	**10^{-3}**	**10^{-2}**
Li^{1+}	**1.6×10^{-5}**	**2.0×10^{-6}**	**1.3×10^{-7}**	**2.5×10^{-8}**	**6.8×10^{-4}**	**6.3×10^{-5}**	**6.4×10^{-6}**	**1.3×10^{-6}**
K^{1+}	**1.6×10^{-5}**	**7.7×10^{-7}**	**1.3×10^{-7}**	**2.7×10^{-8}**	**2.5×10^{-4}**	**3.8×10^{-5}**	**3.3×10^{-6}**	**1.0×10^{-7}**
Ca^{2+}	**1.0×10^{-8}**	**7.4×10^{-9}**	**7.0×10^{-9}**	**3.2×10^{-9}**	**4.6×10^{-8}**	**2.0×10^{-8}**	**7.1×10^{-9}**	**4.8×10^{-9}**
Mg^{2+}	**4.5×10^{-8}**	**1.5×10^{-8}**	**7.0×10^{-9}**	**3.1×10^{-9}**	**4.1×10^{-8}**	**3.5×10^{-8}**	**2.1×10^{-8}**	**3.5×10^{-9}**
Fe^{3+}	**4.8×10^{-9}**	**1.6×10^{-7}**	**2.7×10^{-9}**	**1.7×10^{-9}**	**1.4×10^{-8}**	**4.3×10^{-9}**	**8.0×10^{-9}**	**6.8×10^{-9}**
Al^{3+}	**1.6×10^{-9}**	**1.6×10^{-9}**	**8.3×10^{-10}**	**2.9×10^{-7}**	**9.1×10^{-9}**	**7.7×10^{-9}**	**4.4×10^{-9}**	**4.4×10^{-9}**

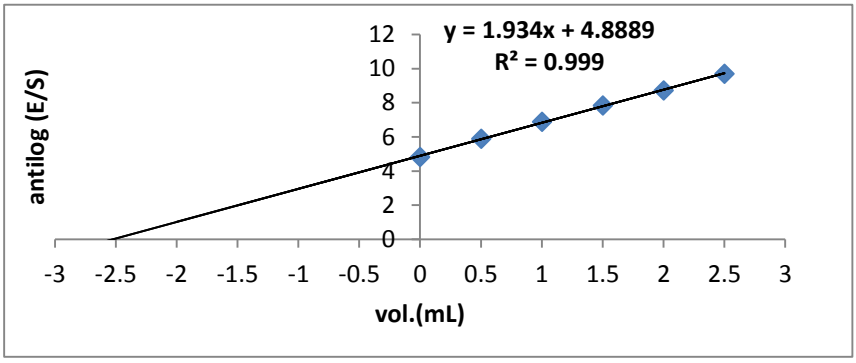
From Table3 it can be seen that selectivity coefficients for all of the species are less than one which point to this drug, monovalent ions and divalent ions and trivalent do not interfere with the trimethoprim determination by these electrodes.

Quantitative Analysis

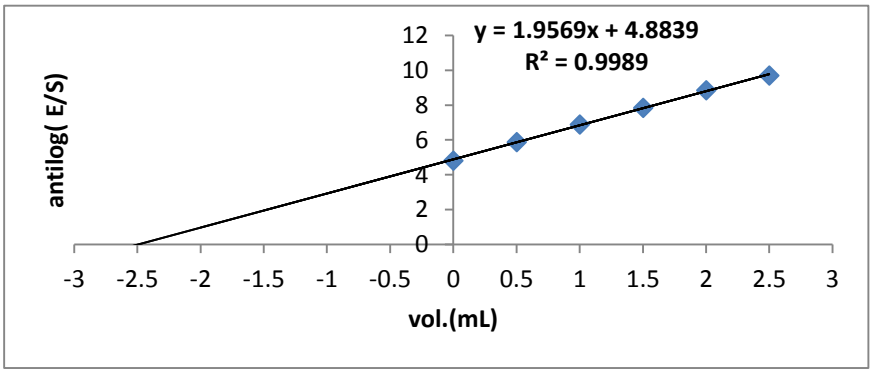
Four potentiometric techniques were used with electrode A(TMP+MP+DBPH) for the determination of trimethoprim, that is titration, multi-standard addition (MSA) standard addition (SA), and direct measurement by using two concentration 10^{-3} and 10^{-4} M of trimethoprim solution. Graph 8, 9 was shown the multi-standard addition (MSA) at concentration 10^{-3} and 10^{-4} M of trimethoprim solutions, and was used 10^{-3} M of molybdophosphoric acid as a titrant for titration shown in Graph 10. The results of the quantitative measurements for trimthoprim solution with relative error, recovery and relative standard deviation and are recorded in Table 4.

Table 4: Potentiometric methods of electrode TMP+ MP+DBPH to evaluate trimethoprim.

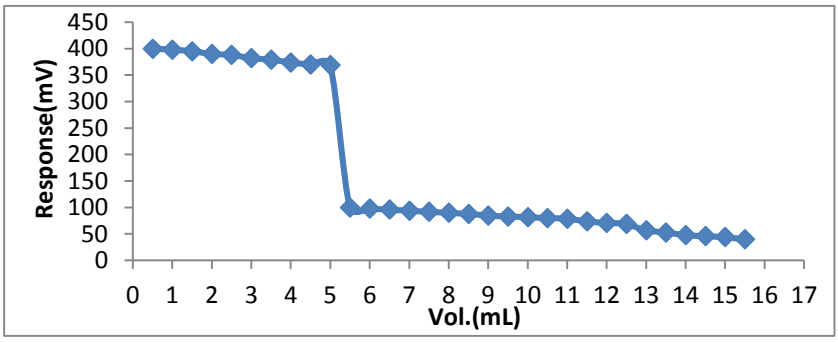
Electrode No.	*Concentration(M)*				
	Sample	*Response by potentiometric method*			
		Direct	*SAM*	*MSA*	*Titration*
TMP+MP+DBPH	1×10^{-3}	0.9676×10^{-3}	0.9896×10^{-3}	0.99647×10^{-3}	0.9901×10^{-3}
	RSD%	0.47	0.36	-	-
	Re%	96.76	98.96	99.64	99.01
	Er%	-3.24	-1.04	-0.36	-0.99
	1×10^{-4}	0.9833×10^{-4}	0.9949×10^{-4}	0.9956×10^{-4}	0.9898×10^{-4}
	RSD%	0.53	0.27	-	-
	RE%	98.33	99.49	99.56	98.98
	Er%	-1.67	-0.51	-0.44	-1.02



Graph 8: Antilog (E /S) versus volume of 10^{-3} M added of trimethoprim using electrode A(TMP+MP+DBPH)



Graph 9: Antilog (E /S)versus volume of 10^{-4} M added of trimethoprim using electrode A(TMP+MP+DBPH)



Graph 10: Titration curve for sample(1×10^{-3}M) TMP with(1×10^{-3}M) MP standard by electrode (TMP+ MP+DBPH)

The direct potentiometric method was applied for the determination of trimethoprim in pharmaceutical tablets (Trimethoprim, Trimoks and Trimol) as recorded in Table 5 using the electrode based on membrane DBPH. The average recovery for trimethoprim determination in tablets was around 98.90% based on an average of 3 measurements for each sample.

Table 5: Sample analysis for tablets using the trimethoprim selective electrode based on DBPH plasticizer using the direct potentiometric method.

Pharmaceutical tablets	Trimethoprim	Trimoks	Trimol
Concentration of TMP(prepared)	1.00×10^{-3}	1.00×10^{-3}	1.00×10^{-3}
Concentration of TMP(found)	0.9815×10^{-3}	0.9989×10^{-3}	0.9868×10^{-3}
RE%	98.15	99.89	98.68
Er%	-1.85	-0.11	-1.32

Comparison Study:

The potentiometric properties with respect to detection limit sensitivity, effect of pH, linear range, and life span of the trimethoprim electrode were compared with those reported for trimethoprim ion selective electrodes were recorded in Table 6.

Depended on this comparison study, trimethoprim electrode offered potentiometric properties comparable in some cases (detection limit, sensitivity, effect of pH, linear range, and life span) with those reported in literatures. Thus, the merits offered by the trimethoprim potentiometric electrodes near to electrodes of trimethoprim previously reported in literature for this drug include high sensitivity, range of PH, lifetime, with detection limit and linearity.

Table 6: Comparison between potentiometric characters of different trimethoprim electrodes.

Parameter	*Refe.16*	*Refe.17*	*Refe.18*	*Refe.19*	*Refe.20*	*This work*
Slope	-	59.7	57 and 58	51.1	59	58.6 and 58.4
Linear range (M)	2×10^{-8}-2×10^{-3}	-	-	3×10^{-5}-2×10^{-2}	2.7×10^{-6}- and 1.0×10^{-2}	1.2×10^{-5}-10^{-2} and 6.1×10^{-5}-10^{-2}
PH range	3.0-7.0	2.0-6.0	2.0-5.7 and 2.0-5.5	-	1.8-6.3	3.0-8.0 and 3.0-6.5
Detection limit(M)	2×10^{-8}	4.0×10^{-7}	-	-	-	2.5×10^{-6} , 6.3×10^{-6}
Life time	-	least 5 weeks.	45 days and 60 days.	-	14 h -15 days	45 days and 2 days
Type of membrane	TMP+PT(film) and photung TMP+silicoutungstate film)	Quartenary ammonium salts.	Ammonium renekate and sodium tetraphenyl borate+di-octyl phthalate	silicotungstate	phosphotungstate	TMP+molybdophosphoric acid+di-butyl phthalate and TMP+molybdophosphoric acid+nitro phenyl octyl ether.

4. CONCLUSION

In this research, we have described a potentiometric method for trimethoprim determination in pharmaceutical drugs using an ion-selective electrode. The best electrode obtained in this study was based on a membrane containing TMP-MP complex and DBPH as a plasticizer. The advantage of the method is its simplicity and selectivity in measuring trimethoprim concentration ranges without any major interference from mono-valent or divalent metal ions and trivalent.

REFERENCES

[1]Zimmer L.,Czarnecki W.,Derivative Spectrophotometric method for Simultaneous Determination of Sulfadimidine and Trimethoprim,SectioDDD,Vol.XXXIII,No.1,3,2012.

[2]Ong S.E.,Kurtzman N.A., Sabatini S., Studies on the mechanism of trimethoprim-induced hyperkalemia, Kindney International,Vol.49, p.p.1372-1378, 1996.

[3]Givianrad M.H., Mohaghian M., Net Analyst Signal Standard Additions Method for Simultaneous Determination of Sulfamethoxazole and Trimethoprim in Pharmaceytical Formulations and Biological Fluids, E-Journal of Chemistry, Vol.9, No.2, p.p.680- 692, 2012.

[4]Madureia T.V., Rocha M.J., Cass Q.B., Tiritan M.E., Development and Optimization of a HPLC-DAD Method for the Determination of Diverse Pharmaceuticals n Estuarine Surface Water, Journal of Chromatographic Science, Vol.48, 2010.

[5]Lazar M., Mouzdahin A., Development of Stability Indicating RP-HPLCS for Simulataneous Estimation of Trimethoprim,Sulfamethoxazole and Methyl parapenin oral Suspension,International Journal of Pharmaceutical Research&Analysis, Vol.4 , p.p.83-89, 2014.

[6]Ahmadi S.H., Kargosha K., Bahadori R., FTIR Spectrometric Determination of Sulphamethoxazole and Trimethoprim in Co-Trimoxazole tablets,Indian Journal of Pharmaceutical Sciences, 1999.

[7]Bagheri A., Khomani S.R., Determination of Trimethoprim Based on Charge-Transfer Complexes Formation, Journal of Applied Chemical Research, Vol.7, No.3, p.p. 25-33 , 2013.

[8]Medina J.R.Miranda M.,Hurtado M., Ramirez A.M.D., Segura J. G.R. Simultaneous Determination of Trimethoprim and Sulfamethoxazole in immediate-Release oral Dosage Forms by First-Order Derivative Spectroscopy:Application to Dissolution Studies, International Journal of Pharmacy and Pharmaceutical Sciences, Vol.5, No.4, 2013.

[9]Alaghaz A.M.A., Farag R.S., Elnawawy M.A.., Ekawy A.D., Synthesis and Spectral Characterization Studies of New Trimethoprim-Diphenylphosphate Metal Complexes, International Journal of Scinces and Research(IJSR), Vol.5(1), 2016.

[10]Abd El-Rhman M.K., Elzanfaly E.S., Ibrahim M.M., Kelani K.M., Ramadan N.K., Ion Selective Membrane Electrodes for the Determination of Mixture of Analgin and Camylofin Dihydrochloride in their Pure Form and Combined Dosage Form,Anal.Bioanal.Electrochem., Vol.9, No.1, p.p.1-14,2017.

[11]Al-Mustafa J.I., Abuo-Dalo M.A., Nassory N.M., Liquid Selective Electrodes for Dextromethorphan Hydrobromide Based on a Molecularly Imprinted Polymer in PVC Matrix Membrane, Int. J. Electrochem. Sci.,Vol.9, p.p.292-303, 2014.

[12]Nassory N., Maki Sh., Al-phalahy B., preparation and potentiometric study of promethazine hydrochloride selective electrodes and their use in determining some drugs, Turk. J. Chem., 32, 539-548, 2008.

[13]Al-Kafaji I.H.M., Al-Bayati Y.K., Synthesis of New Selective Electrodes for the Determination of Metronidazole Benzoate (MNZB) Based on a Molecularly Imprinted Polymer Combined With Poly Vinyl Chloride, International Journal of ChemTech Research, Vol.10 No.3, pp 552-561, 2017.

[14]Arida H., Alrobaian M., Elbeshlawy M., Fatafah A., Al-Sallami G., A New Coated Wire Selective Electrode for Quetiapin in Biological and Pharmaceutical Analysis, International Journal of Electochemical Science,Vol.12, p.p.4120-4133, 2017.

[15]Bassuoni Y.F., Elzanfaly E.S., Essam H.M., Zaazaa H.E., Ion Selective Electrode Approach for In-line Determination of Benzydamine Hydrochloride in Different Matrices of Pharmaceutical Industry, Analytical& Bioanalytical Electrochemistry, Vol.9, No.1, p.p.65-79, 2017.

[16]Li W., Su X., Guo H., We W., Yao S., Preparation and Application of a Trimethoprim Ion –

Selective Piezoelectric Sensors, Analyst, No.124, p.p.91-95, 1999.

[17]Rebelo T.S.C.R., Almeida S.A.A., Guerreiro J.R.L., Montenegro M.C.B.M., Sales M.G.F., Trimethoprim-Selective Electrodes with Molecularly Imprinted Polymers Acting as Ionophores and Potentiometric Transduction on Graphite Solid –Contact, Microchemical Journal, Vol.98, p.p.21-28, 2011.

[18]Ahmed M.A,Elbeshlawy M.M.,Novel Polymeric Membrane Electrodes for Selective Determination of Trimethoprim,Analytical Letters ,Vol.28,Issue 12,1995.

[19]Yao S., Shiao J., Nie L.A trimethoprim-Selective membrane Electrode, Talanta, Vol.34, p.p.983-986, 1987.

[20]Aboudnan M., Shoukry A.F., Issa Y.M., Trimethoprimium-Phosphotungstate Ion Associate as Ion –Exchange For Trimethoprimium Ion –Selective Electrode, Analytical Letters, Vol.29, 1996.