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Analysis of Ketoconazole and Trimetazidine Hydrochloride using ion Selective Electrode

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Abstract—*The performance of two PVC membrane electrodes containing DOP & DBP are described two electrodes are based on the use of DOP & DBP association compounds Ketoconazole is cis-1-acety 1-4 {4-[(2-(2,4-dichlorophenyl)-2(1H-imidazole -1–ylmethyl]-13–dioxolan–4yl) 1- Methoxy] pheny 1 }piperzine(KC)with TPB & PT and trimetazidine Hydrochloride is 1-[(2,3,4-Trimethoxyphenyl 1)methyl 1]–Piperazine Dihydrochloride (TMH) with TPB &PT.*

The developed electrodes were also analysis in some pharmaceutical formulations. The electrodes are characterized by a wide usable concentrations range of 1.01x10^{-5}–1 x 10^{-2} M, Respectively for nearly all the studied electrodes at 25 ^{o}C by the use of ion exchangers membrane method. That can be use for the direct and measurement of Ions and other species. The use of ion–selective electrodes and potentiometric techniques in the analysis of drugs. Substances are reviewed. Ion–exchangers membrane technologies used for the characterization of these membranes are their applications were also reviewed for the benefit of readers. So that they can get all Information about the Ion- exchanger membranes at one platform.

Keyword: *ION EXCHANGER MEMBRANE BIOSENSORS, ELECTROCAMICAL DEVICES .*

1. INTRODUCTION

ION-SELECTIVE ELECTRODES

A CHEMICAL SENSOR IS A DEVICE THAT SELECTIVELY, CONTINUOUSLY AND REVERSIBLY TRANSFORMS CHEMICAL INFORMATION, RANGING FROM THE CONCENTRATION OF A SPECIFIC SAMPLE COMPOPNENT TO A TOTAL COMPOSITION, INTO A SINGLE OF A FORM THAT CAN BE PROCESSED BY AN INSTRUMENT (SUCH AS VOLTAGE, CURRENT OR FREQUENCY). ION-SELECTIVE ELECTRODES (ISES) BELONG TO THE MOST WIDELY APPLIED CHEMICAL SENSORS.

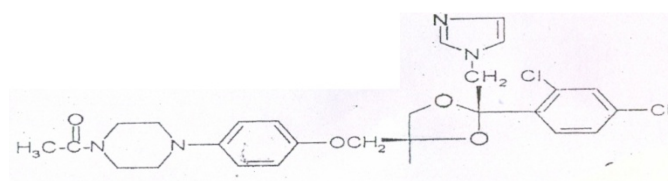
TYPE OF ION-SELECTIVE ELECTRODES

A. GLASS ELECTRODES
   a. PH ELECTRODES
   b. GLASS ELECTRODES FOR OTHER CATIONS
B. LIQUID-MEMBERANCE ELECTRODES
C. ION-EXCHANGER ELECTRODES
D. NEUTRAL CARRIER ELECTRODES
E. ENZYME–BASED ELECTRODES
F. SOLID–STATE ELECTRODES
G. COATED-WIRE ELECTRODES (CWES)
H. ION SELECTIVE FIELD EFFECT TRANSISTORS (ISFET)
I. GAS–SENSING ELECTRODES

2. METHOD & MATERIAL

There are some compound like
KETOCONAZOLE (KC)

Ketoconazole, Cis-1-acety 1-4 {4-[[2-(2,4-dichlorophenyl)-2 (1H-imidazole–1-ylmethyl)-13-dioxolan-4yl] 1 methyoxy] pheny1} piperazine (KC). Introduction of ketoconazole into medical practice in the early 1970s initiated a new area of antifungal therapy. The availability of an orally absorbed drug with low toxicity permitted outpatient therapy of deep mycoses, long-term prophylaxis of immunocompromised patients and treatment of low-morbidity conditions.



Ketoconazole (KC)

Ketoconazole is a potent systemic antimycotic used to treat apportunistic infections in AIDS patients as well as the treatment of a wide range of endocrinological and lipid metabolism disorders. The potent inhibitory effects on oxidative metabolism have also made this compound a useful chemotherapeutic agent for prostate cancer.

Ketoconazole is an imidazole antifungal administered topically in the treatment of fungal skin infections and the most recent and strongest of all imidazole drugs which has been used in the treatment of tinea infections. It has also activity against a great number of fungi and some Gram-Positive microorganisms. The proprietary preparations are Nizoral tablets and Nizoral Cream.

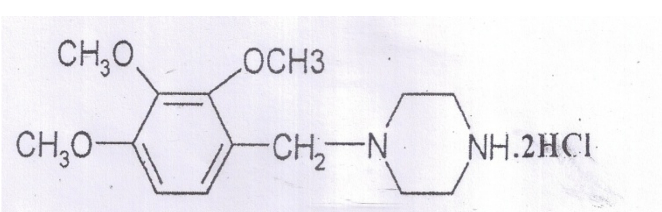
TABLE 1: PERFORMANCE CHARACTERISTICS OF KC-ELECTRODES AT DIFFERENT MEMBRANE COMPOSITION

Ion Exchangers	**Membrane Composition(%)(W/W)**				**Slope (mV/decade)**	**Usable concentration range (mol/L)**	**RDS* (%)**
		DO	**DBP**	**PVC**			
KC-TBP	3.0	48.50	--	48.50	43.5	1.00x10-5–8.24x10-3	1.13
	5.0	47.50	--	47.50	46.3	2.25x10-5 -7.16x10-3	0.96
	7.5	46.25	--	46.25	50.0	3.16x10-5 -5.0x10-3	0.75
	10.0	45.00	--	45.00	52.2	2.00x10-5 -7.94x10-3	0.91
	12.5	43.75	--	43.75	48.4	2.00x10-5-7.94x10-3	0.93
	15.0	42.50	--	42.50	45.7	3.16x10-5 -8.9x10-3	1.30
	3.0	--	48.50	48.50	55.4	3.15x10-5-7.94x10-3	0.90
***	5.0	--	47.50	47.50	56.3	1.00x10-5-8.9x10-3	0.73
	7.5	--	46.25	46.25	55.8	3.16x10-5-7.94x10-3	0.81
	10.0	--	45.00	45.00	51.5	2.80x10-5-7.08x10-3	0.69
	12.5	-	43.75	43.75	47.7	1.00x10-5-7.94x10-3	1.23
	15.0	--	42.50	42.50	36.0	6.31x10-5-1.0010-3	1.75
KC-PT	3.0	48.50	--	48.50	42.5	2.00x10-5-1.51x10-3	1.68
	5.0	47.50	--	47.50	53.3	3.21x10-5-5.34x10-3	1.29
	7.5	46.25	--	46.25	58.0	5.16x10-6-1.2510-3	0.86
	10.0	45.00	--	45.00	53.5	2.16x10-5-8.63x10-3	0.54
	12.5	43.75	--	43.75	46.6	2.00x10-5-7.94x10-3	0.68
	15.0	42.50	--	42.50	45.0	4.37x10-5-4.51x10-3	1.08
	3.0	-	48.50	48.50	45.4	3.98x10-5-1.00x10-3	0.76
	5.0	--	47.50	47.50	46.3	2.00x10-5-1.58x10-3	0.65
**	7.5	--	46.50	46.25	53.8	1.26x10-5-2.00x10-3	0.56
	10.0	--	45.50	45.00	51.5	1.00x10-5-2.50x10-3	0.87
	12.5	--	43.75	43.75	47.7	3.16x10-5-2.51x10-3	1.37
	15.0	--	42.50	42.50	36.0	7.24x10-5-3.16x10-3	1.63

*Relative standard deviation (Five determination)
*Optimum Composition

3. TRIMETAZIDINE HYDROCHLORIDE (TMH)

TRIMETAZIDINE HYDROCHLORIDE IS 1-{(2,3,4-Trimethoxypheny1)methy1}-piperazine dihydrochloride (TMH). It is used in angina pectoris and in ischaemia of neurosensorial tissues as in menier’s diseases. Trimetazidine hydrochloride with proprietary preparations vastarel, which has been given in divided doses of 40 to 60mg daily by mouth as anti -anginal vasodilator drug.



Experimental

The conventional sensitive electrodes were prepared as described previously. Trials make to attain the optimum membrane composition, result in selecting membranes contained the optimum percentages (in wt %) ion-pairs or ion-associates, PVC and DOP or DBP. The membrane components (totaling 350 mg) were dissolved in THF (10.00) and poured into a 7.5 cm Petridish. Overnight evaporation of the solvent yielded a membrane 0.1 mm thickness, as visually determined by an optical microscope. For each electrode, a disk with 14 mm diameter was punched from the membrane and glued to the polished end of a 2 cm plastic cap attached to one end of a 10 cm glass tube. The electrodes were than filled with 0.1 M Nacl + 10^{-3} M drug solution and Ag/AgCl wire was immersed in this solution. The resulting electrodes were preconditioned by soaking them for appropriate time in 10^{-3} M drug solution.

4. RESULT AND DISCUSSION

The Four electrodes have been prepared and investigated in the present study. The electrodes were based on the incorporation of the ion-exchangers in PVC matrix using DOP or DBP as a platicizer. The optimum composition of membrane were : (5.0% KC-TPB, 47.5% DBP and 47.5% PVC), (7.5 % KC-PT, 46.25 % DOP and 46.25 % PVC), (5.0% TMH -TBP, 47.5% DOP and 47.5% PVC) and (10.0 % TMH-PT, 45.0 % DBP and 45.0 % PVC), respectively with slopes 56.3, 58.0, 56.5 and 57.8, mV per concentration decade for KC-TPB,KC-PT, TMH-TPB,and TMH -PT, respectively. These compositions have been used to carry out all the subsequent studies.

The electrodes are characterised by a wide usuable concentration range of 1.01 x 10^{-5}-1.0 x10^{-2} M, respectively for nearly all the studied electrodes at 25°C.

A method for regeneration of the exhausted electrodes was applied successfully in case of all electrodes.

The change of P^H does not affect the potential readings of the studied electrodes within the P^H ranges, 4.0-8.0, 2.0-9.0, 3.9-9.0 and 3.5-10.0 for KC-TPB, KC-PT, TMH-TPB, TMH-PT, electrodes, respectively.

TABLE 3: PERFORMANCE CHARACTERISTICS OF TMH-ELECTRODES AT DIFFERENT MEMBRANE COMPOSITIONS

Ion-Exchanger	Membrane Composition (%) (w/w)				Slope (mV/decade)	Usable concentration range (mol/L)	RSD* (%)
		DO	DBP	PVC			
TMH-TPB	1.0		--		50.0	2.01 x 10^{-5} - 1.00 x 10^{-3}	0.58
	2.0	49.00	--	49.00	53.0	5.01 x 10^{-6} - 1.00 x 10^{-3}	0.71
	3.0	48.50	--	48.50	55.8	1. 00 x 10^{-5} - 4.7 x 10^{-3}	0.66
**	5.0	47.50	--	47.50	56.5	1.00 x 10^{-5} -1.26 x 10^{-3}	0.75
	7.0	46.50	--	46.50	55.2	2.00 x 10^{-5} - 1.00 x 10^{-3}	0.63
	10.0	45.50		45.50	53.4	4.90 x 10^{-5} - 5.25 x 10^{-3}	0.54
	2.0	-	49.00	49.00	51.0	1.00 x 10^{-5} - 1. 00 x 10^{-3}	0.89
	3.0	-	48.50	48.50	52.0	1.00 x 10^{-5} - 1.00 x 10^{-3}	1.12
	5.0	--	47.50	47.50	54.2	2.00 x 10^{-5} - 1.00 x 10^{-3}	0.93
	7.0	--	46.50	46.50	53.0	2.0 x 10^{-5} - 1.58 x 10^{-3}	0.76
	10.0	--	45.00	45.00	53.0	2.00 x 10^{-5} - 2.51x 10^{-3}	0.62
	13.0	--	43.50	43.50	50.6	3.16 x 10^{-5} - 2.82 x 10^{-3}	0.79
TMH-PT	3.0	48.50	--	48.50	54.2	1.00 x 10^{-5} - 2.39 x 10^{-3}	0.95
	5.0	47.50	--	47.50	54.0	1.00 x 10^{-5} - 4.57 x 10^{-3}	1.12
	7.0	46.25	--	46.25	57.3	5.01 x 10^{-6} - 4.57 x 10^{-3}	0.83
	10.0	45.00	--	45.00	55.1	2.00 x 10^{-5} - 4.57 x 10^{-3}	0.62
	12.0	44.00		44.00	52.0	5.01x 10^{-6} - 4.57 x 10^{-3}	0.81
	15.0	42.50		42.50	49.6	5.01 x 10^{-6} - 4. 57 x 10^{-3}	0.97
	3.0	--	48.50	48.50	53.5	5.0 1 x 10^{-6} - 2.40 x 10^{-3}	0.86
	5.0	--	47.50	47.50	56.2	5.0 1x 10^{-6} - 2.40 x 10^{-3}	0.74
	7.0	--	46.25	46.25	57.1	1.00 x 10^{-5} - 3. 16 x 10^{-3}	0.51
**	10.0	--	45.00	45.00	57.8	1.00 x 10^{-5} - 4.57 x 10^{-3}	0.46
	13.0	--	43.50	43.50	52.3	2.00 x 10^{-5} - 2.40 x10^{-3}	0.72
	15.0	-	42.50	42.50	50.9	2.00 x 10^{-5} - 2.40 x 10^{-3}	0.84

*Relative standard deviation (five determinations)
**Optimum Composition

TABLE 3: PERFORMANCE CHARACTERISTICS OF TMH-ELECTRODES AT DIFFERENT MEMBRANE COMPOSITIONS

Ion-Exchanger	Membrane Composition (%) (w/w)				Slope (mV/decade)	Usable concentration range (mol/L)	RSD* (%)
		DO	DBP	PVC			
TMH-TPB	1.0		--		50.0	2.01 x 10^{-5} - 1.00 x 10^{-3}	0.58
	2.0	49.00	--	49.00	53.0	5.01 x 10^{-6} - 1.00 x 10^{-3}	0.71
	3.0	48.50	--	48.50	55.8	1. 00 x 10^{-5} - 4.7 x 10^{-3}	0.66
**	5.0	47.50	--	47.50	56.5	1.00 x 10^{-5} -1.26 x 10^{-3}	0.75
	7.0	46.50	--	46.50	55.2	2.00 x 10^{-5} - 1.00 x 10^{-3}	0.63
	10.0	45.50		45.50	53.4	4.90 x 10^{-5} - 5.25 x 10^{-3}	0.54
	2.0	-	49.00	49.00	51.0	1.00 x 10^{-5} - 1. 00 x 10^{-3}	0.89
	3.0	-	48.50	48.50	52.0	1.00 x 10^{-5} - 1.00 x 10^{-3}	1.12
	5.0	--	47.50	47.50	54.2	2.00 x 10^{-5} - 1.00 x 10^{-3}	0.93
	7.0	--	46.50	46.50	53.0	2.0 x 10^{-5} - 1.58 x 10^{-3}	0.76
	10.0	--	45.00	45.00	53.0	2.00 x 10^{-5} - 2.51x 10^{-3}	0.62
	13.0	--	43.50	43.50	50.6	3.16 x 10^{-5} - 2.82 x 10^{-3}	0.79
TMH-PT	3.0	48.50	--	48.50	54.2	1.00 x 10^{-5} - 2.39 x 10^{-3}	0.95
	5.0	47.50	--	47.50	54.0	1.00 x 10^{-5} - 4.57 x 10^{-3}	1.12
	7.0	46.25	--	46.25	57.3	5.01 x 10^{-6} - 4.57 x 10^{-3}	0.83
	10.0	45.00	--	45.00	55.1	2.00 x 10^{-5} - 4.57 x 10^{-3}	0.62
	12.0	44.00		44.00	52.0	5.01x 10^{-6} - 4.57 x 10^{-3}	0.81
	15.0	42.50		42.50	49.6	5.01 x 10^{-6} - 4. 57 x 10^{-3}	0.97
	3.0	--	48.50	48.50	53.5	5.0 1 x 10^{-6} - 2.40 x 10^{-3}	0.86
	5.0	--	47.50	47.50	56.2	5.0 1x 10^{-6} - 2.40 x 10^{-3}	0.74
	7.0	--	46.25	46.25	57.1	1.00 x 10^{-5} - 3. 16 x 10^{-3}	0.51
**	10.0	--	45.00	45.00	57.8	1.00 x 10^{-5} - 4.57 x 10^{-3}	0.46
	13.0	--	43.50	43.50	52.3	2.00 x 10^{-5} - 2.40 x10^{-3}	0.72
	15.0	-	42.50	42.50	50.9	2.00 x 10^{-5} - 2.40 x 10^{-3}	0.84

*Relative standard deviation (five determinations)
**Optimum Composition

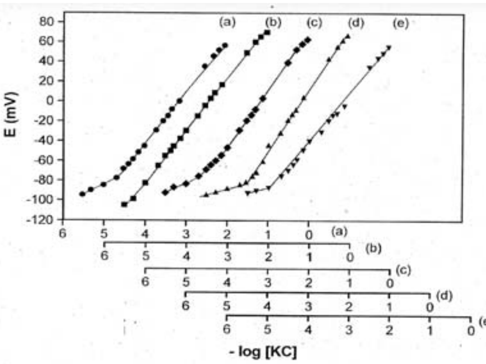


Fig. 1. Calibration graphs of KC-TPB electrodes at different membrane compositions, where (a) 3%, (b) 5%, (c) 7%, (d) 10% and (e) 13% ion-exchanger

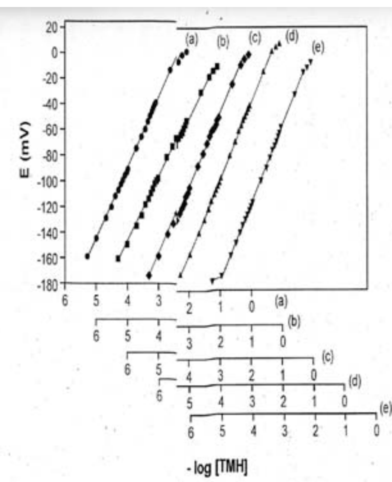


Fig. 3. Calibration graphs of TMH-PT electrodes at different membrane compositions, where (a) 3%, (b) 5%, (c) 7%, (d) 10% and (e) 13% ion-exchanger

The study of the effect of temperature change on the potential response of the electrodes showed that they are thermally stable over a wide range of temperature (20-60°C). The thermal coefficient of the electrodes are 0.00095, 0.00098, 0.00052 and 0.00113V/°C for KC-TPB, KC-PT, TMH-TPB, TMH-PT, respectively. This reveals that the electrodes have high thermal stability within the usable temperature range.

The investigated drugs were also determined in aqueous solution, using potentiometric titrations, conductimetric titrations and by applying the standard additions method. The study showed that the electrodes under investigation are highly selective even in the presence of some in organic cations, sugars, amino acids and component of the drug formation.

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