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Analysis of Ketoconazole and Piribedil Using Ion Selective Electrodes

Sandhya Chaudhary[1] and Nirmala Sisodia[2]
[1]*Department of Chemistry, NREC College, Khurja, Bulandshahar (U.P.)-203131*
[2]*Department Of Chemistry, SBMT College, Bulandshahar (U.P.)-203131*

Abstract: *The general performance characteristics of two PVC membrane electrodes containing DOP and DBP are described. Two electrodes are based on the use of DOP and DBP association compounds ketoconazole is cis-1-acety1-4{4-[[2-(2,4-dichlorophenyl)-2(1H-imidazole-1-ylmethyl)-1,3-piperazine (KC) with and Piribedil is 1-(3,4-methylenedioxybenzy1)-4,2-pyrimidyl)piperazine (PD) with tetraphenylbroate and PT. The developed electrodes were also analyses in some pharmaceutical formulations. The electrodes are characterized by a wide usable concentrations range of 1.01 x 10^{-5}-1 x 10^{-2} M, respectively for nearly all the studied electrodes at 25^0C 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 subtances are reviewed. Ion-exchangers membrane technologies used for the characterization of these membrane 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.*

I. Introduction

A chemical sensor is a device that selectivity, continuously and reversibly transforms chemical information, ranging from the concentration of a specific sample component 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[1].

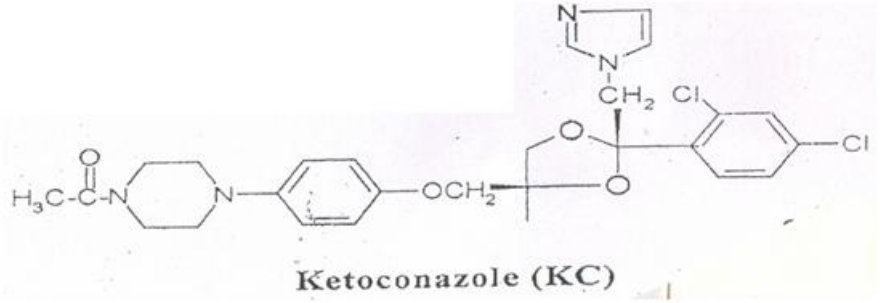
They have two functions, namely, selection and transduction. The former assures the required selectivity behavior of the ion-selective part of the sensor through chemical interactions with charged species of the analyte and the latter the transformation of these interactions into an electrochemical potential of the measuring ISE relative to a reference electrode. Since the signal is proportional to the logarithm of the ion activity, it generally covers a large dynamic range. The field of the electrochemical sensors is perhaps one of the most fruitful, exciting and interdisciplinary areas of research in analytical chemistry.

Herein present studies, two new Ketoconazole and Piribedil compounds using Ion Selective electrodes have been analyzed.

II. Method And Material

There are two compound have been analyzed Ketoconazole (KC) and Piribedil (PD), 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.

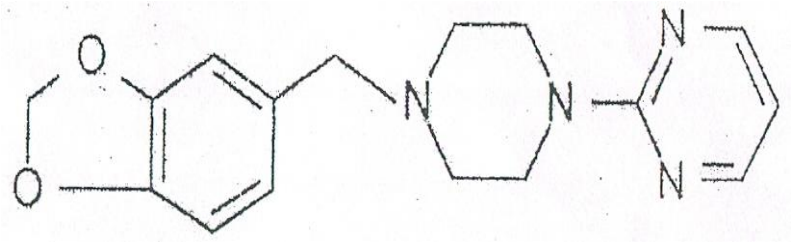
Ketoconazole is a potent systemic antimycotic used to treat apportunistic infections in AIDS patients as well as the treatment of a wide range of endocrinological and lipid metabolism disorders. The potent inhibitory effects on oxidative metabolism have also made this compound a useful chemotherapeutic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



Ketoconazole (KC)

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.

Piribedil is 1-(3, 4-methylenedioxybenzy1)-4-2-pyrimidy1) piperazine (PD, has been shown to be active as a peripheral vasodilator.



Piribedil (PD)

Piribedil is a non-ergot dopamine agonist that has been given by mouth in the treatment of parkinsonism and in circulatory disorders. Piribedil is a dopamine Dragonist while its metabolite is reported to act on D1 receptors. It has been mainly used as an adjunct to levodopa therapy and appears to act more on termor than on other symptoms of Parkinson's disease, althought it was noted that most of the evidence for this came from uncontrolled studies.

Piribedil has been tried in the treatment of depression, its adverse effects reported include nausea and vomiting, dizziness, confusion, drawsiness, hypothermia, dyskinesias and occasional change in liver function. The proprietary preparation is Trivastal tablets.

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 com Petri dish. 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.

III. Results 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% PD-TPB, 47.5% DBP and 47.5% PVC), (5.0% PD-PT, 47.5% DOP and 47.5% PVC), respectively with slopes 56.3, 58.0, 57.1, 60.0, 56.5, 57.8, 60.2 and 59.1 mV per concentration decade for KC-TPB, PD-TPB, PD-PT, respectively. These compositions have been used to carry out all the subsequent studies.

The electrodes are characterized by a wide useable 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 pH does not affect the potential readings of the studied electrodes within the pH ranges (from the table 1 and 2) 4.0-8.0, 2.0-9.0, 4.0-9.0, 2.5-8.5, 3.9-9.0, 3.5-10.0, 4.0-11.0 and 3.3-9.6 or KC-TPB, KC-PT, PD-TPB, PD-PT, electrodes, respectively.

From the figure 1 and 2 shows 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, 0.00101, 0.00126V/°C for KC-TPB, KC-PT, PD-TPB, PD-PT, respectively. This reveals that the electrodes have high thermal stability within the usable temperature range.

The investigated drugs were determined in aqueous solution, using potentiometric titrations, conductiometric 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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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

Table 2: performance characteristics of pd-electrodes at different membrane composition

Ion Exchangers	Membrane Composition(%)(W/W)				Slope (mV/decade)	Usable concentration range (mol/L)	RDS* (%)
	DO	DBP	PVC				
PD-TBP	2.0	49.00	--	49.00	36.7	$5.01x10^{-6}$-$5.01 x 10^{-4}$	1.14
	3.0	48.50	--	48.50	42.5	$1.00x10^{-5}$-$6.31x10^{-3}$	0.81
	5.0	47.50	--	47.50	45.0	$2.16x10^{-5}$-$1.01x10^{-2}$	0.70
	7.0	46.50	--	46.50	44.2	$2.00x10^{-5}$-$1.74x10^{-2}$	1.25
	10.0	45.50	--	45.00	35.4	$2.00x10^{-5}$-$1.00x10^{-2}$	1.31
	2.0	--	49.00	49.00	50.3	$3.15x10^{-5}$-$5.01x10^{-3}$	0.83
	3.0	--	48.50	48.50	52.3	$2.00x10^{-5}$-$5.01x10^{-2}$	0.57
**	5.0	--	47.50	47.50	57.1	$2.00x10^{-5}$-$1.00x10^{-2}$	0.49
	7.0	--	46.50	46.50	50.0	$1.00x10^{-5}$-$3.98x10^{-2}$	0.74
	10.0	--	45.50	45.00	46.7	$6.31x10^{-5}$-$1.00x10^{-2}$	0.92
PD-PT	1.0	49.50	--	49.50	53.2	$2.00x10^{-5}$-$4.47x10^{-2}$	0.68
	3.0	48.50	--	48.50	57.0	$1.00x10^{-5}$-$6.03x10^{-3}$	0.46
	5.0	47.50	--	47.50	60.0	$1.02x10^{-5}$-$1.00x10^{-2}$	0.76

	7.0	46.50	--	46.50	56.1	$2.00x10^{-5}$-$7.94x10^{-3}$	0.93
	10.0	45.50	--	45.00	54.0	$2.00x10^{-5}$-$7.94x10^{-3}$	0.81
	3.0	--	48.50	48.50	52.4	$2.51x10^{-5}$-$7.94x10^{-4}$	0.94
	5.0	--	47.50	47.50	55.2	$2.00x10^{-5}$-$7.94x10^{-3}$	0.75
	7.0	--	46.50	46.25	57.3	$2.00x10^{-5}$-$1.00x10^{-3}$	0.90
	10.0	--	45.50	45.00	54.5	$2.00x10^{-5}$-$1.00x10^{-3}$	0.69
	12.5	--	43.75	43.75	50.2	$2.16x10^{-5}$-$6.31x10^{-4}$	1.05

*Relative standard deviation (Five determinations)
*Optimum Composition