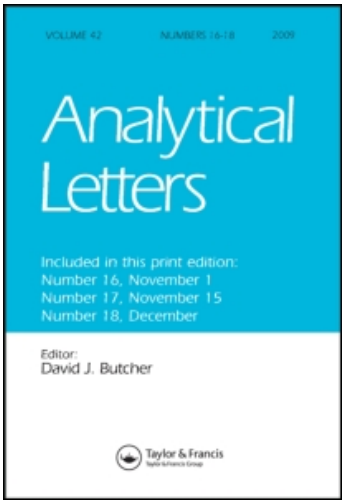

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Fabrication of Potentiometric Sensors for the Selective Determination of Ketoconazole

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Fabrication of Potentiometric Sensors for the Selective Determination of Ketoconazole

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Abstract: The fabrication and analytical applications of two types of potentiometric sensors for the determination of ketoconazole (KET) are described. The sensors are based on the use of KET-molybdophosphoric acid (MPA) ion pair as electroactive material. The fabricated sensors include both polymer membrane and carbon paste electrodes. Both sensors showed a linear, stable and near Nernstian slope of 57.8 mV/decade and 55.2 mV/decade for PVC membrane and carbon paste sensors respectively over a relatively wide range of KET concentration ($1 \times 10^{-2} - 5 \times 10^{-5}$and $1 \times 10^{-2} - 1 \times 10^{-6}$). The sensors showed a fast response time of <30 sec and <45 sec. A useful pH range of 3–6 was obtained for both types of sensors. A detection limit of 2.96×10^{-5}M was obtained for PVC membrane sensor and 6.91×10^{-6} M was obtained for carbon paste sensor. The proposed sensors proved to have a good selectivity for KET with respect to a large number of ions. The proposed sensors were successfully applied for the determination of KET in pharmaceutical formulations. The results obtained are in good agreement with the values obtained by the standard method.

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Keywords: Carbon paste sensor; Ketoconazole; Molybdophosphoric acid; Pharmaceutical formulations; Polymeric membrane sensor; Potentiometry

INTRODUCTION

Ketoconazole, [(±)-*cis*-1-acetyl-4-(4-{[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy} phenyl) piperazine] is an orally active, antimycotic agent from the class of imidazole derivatives. It is active against *Candida* spp., *Cryptococcus neoformans*, and *Pseudallescheria boydi*. It is used to treat a wide variety of dermal and systematic mycoses and has the advantage over other imidazole derivatives of producing adequate sustained blood levels following oral administration (Abounassif and El-shazly 1989; Farhadi and Maleki 2001). Ketoconazole is the only member of the imidazole derivatives currently used for the treatment of systemic infections. The continually increasing number of patients suffering from mycoses due to decreased immunity (AIDS, organ transplantations, etc.) has led to a rather frequent application of pharmacologically active agents from this class (Vojic et al. 2005).

Ketoconazole is used as a broad-spectrum antifungal agent for the treatment or prevention of fungal infections especially against thrush, gastrointestinal infections, and infections of the skin, nails, and scalp. It is also topically used in the formulation of cosmetic creams and in shampoos as an antidandruff agent.

Several analytical methods have been developed for quantitative determination of ketoconazole. These include visible spectrophotometry (Abdel-Gawad 1997), ultraviolet (UV) spectrophotometry (El-Shabouri et al. 1998), spectrofluorimetry (El-Shanawany et al. 1997), thin-layer chromatography (Roychowdhury et al. 1996), supercritical fluid chromatography with UV detection (Ashraf-Khorassani et al. 1995), capillary electrophoresis with diode array detection (Arranz et al. 2000), high-performance liquid chromatography (HPLC) using different detection modes such as UV (Heyden et al. 2002), diode array (Koves 1995), and electrochemical detection (Hoffman et al. 1988), and stripping voltammetric and polarographic techniques (Arranz et al. 2003). However, most of these methods require expensive and sophisticated instruments and are time- consuming. Hence it is worthwhile to develop a simple and sensitive method for the analysis of this drug.

Ion selective electrodes have found useful applications (Abbas et al. 2000; Abbas et al. 2001; Hassan et al. 2000; Durust and Meyerhoff 2001; Shamsipur et al. 2002; Malinowska et al. 1999; Ion et al. 2001; Baniwal et al. 1999; Badawy et al. 1986) that are simple, economical, and applicable over a wide range of concentration and offer sufficient

selectivity to the drug in presence of pharmaceutical excipients. The high selectivity of these electrodes imparts a great advantage over other techniques. Modern ion selective electrodes based on material transport across a specific membrane are now widely used in the determination of trace amounts of analytes. The material transport includes both neutral and charged complex species or simple ions (El- Kosasy et al. 2005). A further advantage is that they are relatively simple and cheap to develop, set up, and run.

In continuation of our work on drug analysis (Girish Kumar et al. 1997, 2005, 2006a, 2006b, 2007, Girish Kumar, Augustine, et al. 2007), an attempt has been made to develop two types of potentiometric sensors for the quantitative determination of KET. The present work describes the fabrication of potentiometric sensors for the determination of ketoconazole in pure form and in dosage forms. The reported sensors include a plastic membrane sensor and a carbon paste sensor by incorporating the ion-pair KET–MPA, and the performance characteristics were studied. The sensors were successfully applied for the determination of KET in pure solutions and pharmaceutical preparations, and the results obtained are in good agreement with those obtained by the official method.

EXPERIMENTAL

Reagents and Materials

All the chemicals used were of analytical grade. Molybdophosphoric acid (MPA), dibutyl sebacate (DBS), and all of the metal salts used were obtained from Merck. Bis (2-ethyl hexyl) phthalate (BEP), bis (2-ethyl hexyl) sebacate (BES), bis (2-ethyl hexyl) adipate (BEA), and di-n-butyl phthalate (DBP) were obtained from Lancaster (UK), tetrahydrofuran (THF) from local chemical suppliers (s.d. fine-chem, India), and graphite powder (< 150 micron) from Aldrich. Pure-grade KET was obtained as a gift sample. Pharmaceutical preparations (Ketovate [Bal Pharma, India] and Ketozole [Rexcel, India]) were purchased from local market.

Apparatus

All emf measurements were carried out using the following cell assembly. A saturated calomel electrode (SCE) was used as the external as well as the internal reference electrode. The electrochemical cell assembly may be represented as follows:

For Membrane Sensor

Saturated calomel electrode/internal filling solution (1×10^{-1} M NaCl solution + 1×10^{-3} M drug solution)/PVC membrane/test solution/KCl salt bridge//saturated calomel electrode.

For Carbon Paste Sensor

Reference electrode/test solution/graphite electrode for carbon paste sensor.

A Metrohm 781 ion meter was used for potential measurements. All emf measurements were carried out at 25 ± 1°C.

Synthesis of the Ionophore

The KET–MPA ion association was prepared by mixing 25 ml 10^{-2} M KET with 25 ml 10^{-2} M MPA solutions. The mixture was then shaken well for 10 min and the produced precipitate was filtered through a Whatman filter paper, washed thoroughly with distilled water, dried at room temperature, and stored in a desiccator. The composition of the ion association was confirmed by elemental analysis to be 1:1 (KET: ion pairing reagent). The elemental analysis data obtained for the ion associations are as follows:

KET-MPA ion association
Found(%) : C, 38.12; H, 7.58; N, 3.75
Calculated(%) : C, 38.06; H, 7.53; N, 3.76

Fabrication of KET Membrane Sensor

The membrane electrode was constructed according to the Craggs procedure (Girish Kumar et al. 2007). The membrane composition was studied by varying the percentages of (w/w) of the ion pair, PVC, and plasticizer, until the optimum composition that exhibits the best performances was obtained. The PVC membrane was prepared by dissolving the required amount of the ion-pair, plasticizer, and PVC in 5–7 ml of THF. The mixture was then poured into a petri dish and allowed to stand overnight for slow evaporation of solvent and formation of the sensing membrane. Small portions of the membrane were cut and glued to one end of a glass tube. The electrode body was filled with an inner filling solution containing NaCl (10^{-1} M) and KET (10^{-3} M). The finished

electrode was conditioned in KET solution (10^{-3} M) for 24 h. The electrode was washed with distilled water before measurement.

Fabrication of KET Carbon Paste Sensor

The carbon paste was prepared by mixing the required amount of the ion pair (KET–MPA) with spectroscopic graphite powder and acetone. The resulting mixture was allowed to stand for the slow evaporation of acetone. Plasticizer was added to the carbon paste and the mixture was thoroughly mixed in a mortar until it was uniformly wetted. A Teflon holder with a hole at one end for the carbon paste filling served as the electrode body. Electrical contact was made with a brass rod through the center of the electrode holder. The electrode surface was polished using a filter paper to produce a reproducible working surface. The sensor was conditioned by soaking in a 10^{-3} M solution of KET solution.

Procedure

Standard solutions of the analyte were prepared by serial dilution of stock solution. The potential of each sample solution was directly measured by the developed sensor using the previously mentioned cell assembly. A calibration graph was obtained by plotting EMF (mV) versus log *c*. The calibration graph was used for subsequent determination of unknown KET concentrations.

Application in Pharmaceutical Analysis

Ten tablets of each (Ketovate and Ketozole) were accurately weighed, powdered, and mixed well in a mortar. An appropriate amount of this powder was dissolved in distilled water and then transferred to a volumetric flask after filtration through a Whatman 41 filter paper and diluted to known volume (50 ml). The presently developed sensors were directly immersed into 10 ml of each sample six times, and potential was measured each time. The mean potential was used to evaluate the content of the drug in the tablet from the calibration graph (potential vs. log concentration).

RESULTS AND DISCUSSION

Optimization Studies of the Two Types of Sensors

The nature of the plasticizer has a marked influence on the response slope, linear domain, and selectivity of PVC membrane electrodes. Five

different plasticizers—BEP, BES, DBS, BEA, and DBP—were employed to study their effect on the electrochemical behavior of the membrane. Of the five different plasticizers used, DBP was found to give a near Nernstian response. Hence, the sensor with DBP was selected for further studies. Different ratios of membrane composition were employed to evaluate their effects on the response characteristics of membrane sensor. The results revealed that the best composition was 2.2:40.2:57.6 wt% (ion association: PVC: plasticizer [DBP]). Optimization of the membrane ingredients are presented in Table 1. The sensor gave a linear response behavior within the concentration range $1 \times 10^{-2} - 1 \times 10^{-5}$ MM of KET with a slope of 57.8 mV/decade and a lower detection limit of 2.96×10^{-5} M (Figure 1) at 25°C.

The response characteristics of the carbon paste sensors are largely affected by the nature of the plasticizer used (Ibrahim et al. 2004). All the five plasticizers that were tried for membrane sensors have been tried in the case of carbon paste sensors also. The use of BEP resulted in a Nernstian linear plot over the concentration range $1 \times 10^{-2} - 1 \times 10^{-6}$ M (Figure 2). In the case of other plasticizers used, the slopes of the potentiometric response are much different from the expected Nernstian value. Optimization of composition of the carbon paste sensor is consolidated in Table 2. The results show that the sensor made of 2.4% KET–MPA ion pair exhibits the best performance (slope 55.2 mV/dec, detection limit

Table 1. Optimization of membrane ingredients of PVC membrane sensor

	Composition % (w/w)			
Membrane	Ion-pair %	PVC %	Plasticizer %	Slope mV/decade
A	2	33	65, BEP	53.7
B	2.2	40.2	57.6, BEP	62.8
C	2.4	42	55.6, BEP	73.6
D	2	33	65, DBP	55.6
E	2.2	40.2	57.6, DBP	57.8
F	2.4	42	55.6,DBP	52.2
G	2	33	65, DBS	37.2
H	2.2	40.2	57.6, DBS	52.9
I	2.4	42	55.6, DBS	56.9
J	2	33	65, BES	50.5
K	2.2	40.2	57.6, BES	65.9
L	2.4	42	55.6, BES	73.2
M	2	33	65, BEA	67.9
N	2.2	40.2	57.6, BEA	49.8
O	2.4	42	55.6, BEA	46.5

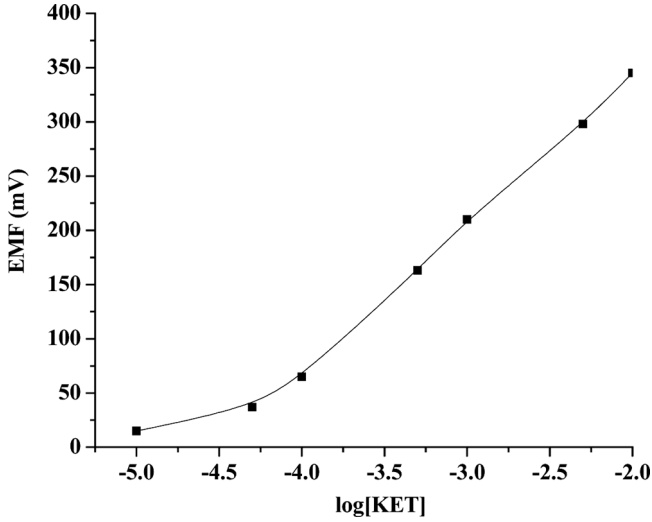

Figure 1. Calibration graph for KET-selective PVC membrane sensor at 25°C.

6.91×10^{-6}, and response time <45 sec). In all subsequent studies, the sensor made of 2.4% KET–MPA ion pair was used in case of carbon paste electrode. The response characteristics of the two types of sensors under investigation are summarized in Table 3.

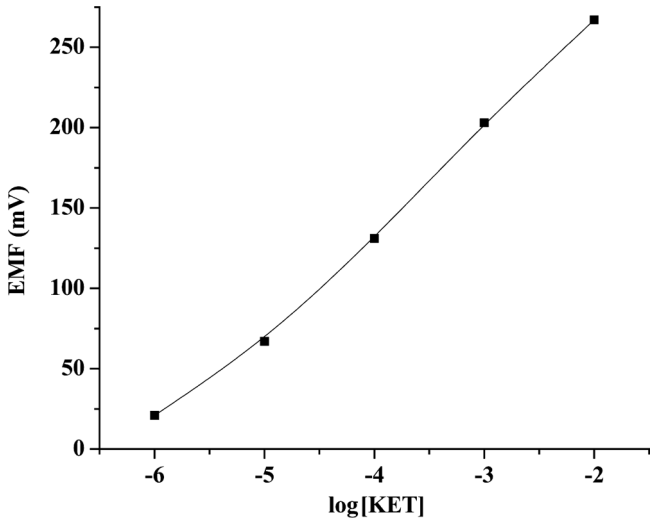

Figure 2. Calibration graph for KET-selective carbon paste sensor at 25°C.

Table 2. Optimization of composition of the carbon paste sensor

	Composition % (w/w)			
Membrane	Ion-pair %	Graphite %	Plasticizer %	Slope mV/decade
A	2	33	65, BEP	50.5
B	2.2	40.2	57.6, BEP	48.6
C	2.4	42	55.6, BEP	55.2
D	2	33	65, DBP	46.7
E	2.2	40.2	57.6, DBP	39.7
F	2.4	42	55.6,DBP	52.2
G	2	33	65, DBS	52.9
H	2.2	40.2	57.6, DBS	37.2
I	2.4	42	55.6, DBS	49.8
J	2	33	65, BES	73.2
K	2.2	40.2	57.6, BES	65.9
L	2.4	42	55.6, BES	63.7
M	2	33	65, BEA	50.4
N	2.2	40.2	57.6, BEA	67.5
O	2.4	42	55.6, BEA	71.2

Effect of Concentration of Internal Filling Solution

The influence of the concentration of the internal filling solution on the potential response of the KET selective membrane sensor was studied. The KET concentration was changed from 1×10^{-4} to 1×10^{-2} M and the EMF vs. log [KET] plot was obtained. It was found that the variation in concentration of the internal solution did not cause any significant difference in the potential. For the carbon paste electrode, there is no need for an internal filling solution. This is one of the significant advantages of the carbon paste sensor.

Table 3. Response characteristics of the developed sensors

Parameter	PVC membrane sensor	Carbon paste sensor
Slope (mV per decade)	57.8	55.2
Linear range (mol L^{-1})	$1 \times 10^{-2} - 5 \times 10^{-5}$	$1 \times 10^{-2} - 1 \times 10^{-6}$
pH range	3–6	3–6
Response time (sec)	<30	<45
Shelf life (weeks)	4	2

Effect of pH

The effect of pH of the test solution (10^{-4} M and 10^{-3} M KET) on the electrode potential was investigated by following the variation in potential with change in pH. The pH was adjusted using different buffer solutions. From the pH studies, it was found that there was no change in the potential response for both the electrodes within the pH range 3–6 (Figures 3 and 4), and hence this was chosen as the working pH range of the sensors.

Selectivity Studies

The selectivity of an ion-pair-based membrane electrode depends on the physicochemical characteristics of the ion exchange process at the membrane–sample solution interface, on the mobility of the respective ions in the membrane, and on the hydrophobic interactions between the primary ion and the organic membrane (Cosofret and Buck 1984). The interference of various substances on the selectivity of the developed sensors has been examined using the fixed interference method (Umezawa et al. 1995). The potentiometric selectivity coefficients were evaluated graphically using the expression $K_{A,B}^{\mathrm{Pot}} = a_A/(a_B)^{ZA/ZB}$, where a_A is the activity

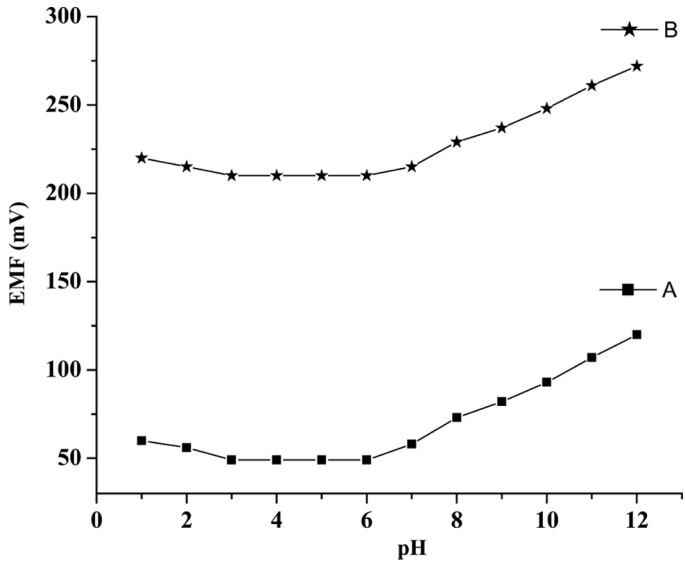

Figure 3. Effect of pH on the cell potential of the KET-selective PVC membrane sensor: 1.0×10^{-4} M (A) and 1.0×10^{-3} M (B).

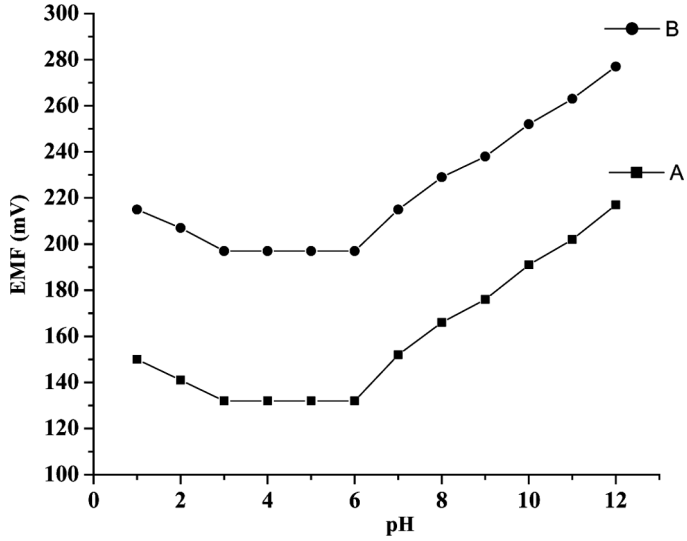

Figure 4. Effect of pH on the cell potential of the KET-selective carbon paste sensor: 1.0×10^{-4} M (A) and 1.0×10^{-3} M (B).

of the primary ion, which is varied; a_B is the activity of the interfering ion, which is fixed; and Z_A and Z_B are charge numbers of the primary ion, A, and of the interfering ion, B. The resulting selectivity coefficients are summarized in Table 4. The results reveal that there were no significant

Table 4. Selectivity coefficient values of various interfering ions, K^{pot}

	K^{pot}	
Interfering ion	PVE membrane sensor	Carban past sensor
NH_4^+	4.6×10^{-3}	2.7×10^{-2}
K^+	3.2×10^{-2}	3.1×10^{-3}
Na^+	6.1×10^{-2}	4.3×10^{-4}
Mg^{2+}	1.7×10^{-3}	5.1×10^{-2}
Co^{2+}	4.2×10^{-3}	2.8×10^{-3}
Ca^{2+}	5.1×10^{-3}	5.7×10^{-3}
Ni^{2+}	4.7×10^{-4}	3.5×10^{-4}
Zn^{2+}	5.9×10^{-4}	3.8×10^{-3}
Urea	2.8×10^{-3}	5.1×10^{-3}
Ascorbic acid	1.6×10^{-3}	4.8×10^{-3}
Glycine	3.4×10^{-3}	2.5×10^{-3}

Table 5. Determination of ketoconazole in tabltes

Sample	Declared amt (mg/tablet)	Method adopted	Found (mg/tablet)	* *SD*	*CV*
Ketovate	200	PVC membrane sensor	196	0.91	0.46
(Bal Pharma,		Carbon paste sensor	195	0.89	0.46
India)		Standard method	198	0.95	0.48
Ketozole	200	PVC membrane sensor	197	0.95	0.48
(Rexcel, India)		Carbon paste sensor	196	0.91	0.46
		Standard method	198	0.98	0.49

*Average of six replicates.

interferences from all of the tested substances, and hence the sensors can be selectively used for the determination of KET.

Response Time and Lifetime of the Sensors

The average response time is the time required for the sensor to reach a stable potential within ± 1 mV of the final equilibrium value. The response time for the KET membrane sensor was less than 30 sec and that of the carbon paste sensor was less than 45 sec. The lifetime of the electrode was investigated by measuring the potentials in standard drug solutions each day. The response slope of the sensors was calculated each time. A Nernstian slope was obtained for a period of 4 weeks in the case of membrane sensor and 2 weeks for carbon paste sensor.

Analytical Applications

The developed sensors were successfully applied for the determination of KET in two commercially available pharmaceutical formulations—Ketovate (Bal Pharma, India) and Ketozole (Rexcel, India)—and the results are summarized in Table 5. The results were compared with those obtained by the standard method (potentiometric titration) (*European Pharmacopoeia* 2002). It has been found that there is satisfactory agreement between the KET content determined by the proposed sensors and the official method.

CONCLUSIONS

Two novel electrochemical sensors have been developed for the determination of KET based on the KET-MPA ion pair as the electroactive

material. It is cost-effective, easy to prepare, and easy to use. The developed sensors are found to have good characteristics in terms of slope, concentration range, detection limit, response time, pH range, and shelf life. The sensors are also found to be highly selective over a number of ions. Further, the developed sensors can be used in the determination of KET in pharmaceutical formulations with very good accuracy and precision.

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