AJHAS

https://albalqajournal.ammanu.edu.jo/SC.aspx
Vol.(1) No.1 Jan 2022

Recived: 1st May 2021
Accepted: 23 Nov 2021
Published online: 30 Nov 2021

Al-Balqa Journal
for Health & Applied Sciences

Micro Titrimetric Determination of Ketoconazole in Both Aqueous and Non-Aqueous Media by Differential Electrolytic Potentiometry Using Metallic Electrodes Coated with Carbon Nanotubes

Abdulaziz N. Amro [1,*]

[1,*] Department of Chemistry, College of Science, Taibah University, Madinah, Saudi Arabia ORCID: 0000-0002-0490-9284
email: abdulazizamro@yahoo.com

Abstract

Differential electrolytic potentiometry was applied for the determination of ketoconazole (KTZ) in pure and tablets forms. Microtitrations were performed in aqueous and non- aqueous media using gold electrodes, antimony electrodes, and silver electrodes coated with carbon nanotubes. The floating catalyst chemical vapor deposition (FC-CVD) method was used for coating silver electrodes with carbon nanotubes. A micro injector was designed to deliver precise volumes of the titrant at sub micro liter levels. Sharp and clear end points were observed for the aqueous titrations of volumes of 2.0 µL and 4.0 µL of 0.1M standard KTZ. The recovery and relative standard deviation indicate high accuracy and comparable precession of the method compared to standard analysis method. However, in case of the non-aqueous titrations of volumes of 25.0 µL and 50.0 µL of 0.01M standard KTZ samples have been found to show sharp end points. Moreover, the samples required for the analysis are much less than those required for any other analytical method.

Keywords

Antimony electrode, Carbon nanotubes, Differential electrolytic potentiometry, Ketoconazole, Microtitrimetry, Silver electrode

Author Biographies

Abdulaziz N. Amro: BSc, MSc, PhD. He obtained his from PhD in Analytical Chemistry (Electroanalytical chemistry) from King Fahd University of petroleum and minerals in Saudi Arabia, and his MSc in analytical chemistry, from Al-Balqa Applied university in Jordan and his BSc in applied chemistry from the Jordan University of Science and Technology in Jordan. He is currently an Associate Professor of Analytical chemistry at the Chemistry Department in Taibah university in Saudi Arabia. His Sub-specialty is in Electroanalytical chemistry. His research interests are in electrochemical determination of pharmaceutical compounds, nanotechnology, and water treatment.

1. Introduction

Conventional titration methods require large chemical volumes. Microtitrimery, will turn titration to be green analytical method consumes very small amount of chemicals, which will save the environment by reducing the quantities of wastes disposed to it.

Differential electrolytic potentiometry (DEP) is electrochemical technique used to locate the end-point in volumetric titration. DEP electrochemical method is based on measuring the potential difference (ΔE) between two identical electrodes polarized by stabelized current during titration process (Bishop, 1956; Bishop, 1958). The first differential endpoint is indicated during zero current potentiometric curve by the presence of sharp peak. One of the major advantages of DEP technique is the absence of a reference electrode, where salt bridge in three electrodes system lead to various difficulties especially in non-aqueous systems (Abdennabi, 1979).

High specific surface area, in addition to the electrical conductivity make carbon nanotubes (CNTs) ideal choice for the modefication of the elecrocemical sensors. Physical and chemical properties of CNTs have been investigated deeply which indicated novel properties for these materials (Ajayan, 1999; Odom, 1998). According to their atomic structure, CNTs showed metal or semiconductor elecreical behavior (Jang et al., 2002; Tekleab et al., 2000). The electronic properties of CNTs modefied electrodes enhance the ability of charge-transfer reactions (Gong et al., 2005; Merkoc et al., 2005;Nugent et al., 2001; Wang, 2005).

Ketoconazole (KTZ), cis-1-acetyl-4- [4- [[2-(2, 4-dichlorophenyl)-2-(1H-imidazole 1ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl] piperazine (Fig. 1) is a highly effective pharmaceutical compound used as broad-spectrum antifungal agent. It is an effective treatment for wide range of systemic and superficial mycoses, furthermore when it is used orally it keeps adequate blood levels compared to other imidazole derivatives (Sa´nchez-Delgado et al., 1993).

Several methods have been reported for KTZ analysis. High performance liquid chromatography (HPLC) was used to determine KTZ in human plasma (Andrews et al.,1981; Chen et al., 2002; Wang et al., 2016), canine plasma (Vertzoni et al., 2006), and shampoo (Heydena et al., 2002). Electroanalytical methods have been reported for KTZ determination using several kinds of bare and chemically modified electrodes (Arranz et al., 2003; Dantas et al., 2010; El Ries et al., 2013; Saleh et al., 2018). Spectrophotometry has been also applied for KTZ analysis which showed high performance (Abdel-Gawad, 1997; Khashaba et al., 2000; Farhadi and Maleki, 2001; Vojic et al., 2005; Jalali and Afshoon, 2008; Rane and Padmaja, 2012; Fraihat, 2014; Fraihat and Bahgat, 2014). Potentiometric titration is the official method for KTZ assay as raw material and in final product (British pharmacopoeia, 2007).

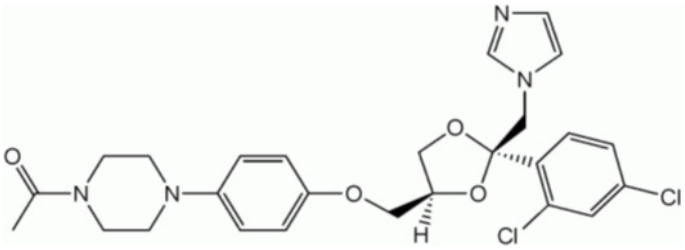

Fig. 1 Ketoconazole structure

In present times, a microtitrimetry setup was designed by fabricating a microliter injector to deliver accurate volumes in microliter level. Pair of metallic electrodes were fabricated then accommodated in especially designed micro cell to be used for mark – space bias AC -DEP. Chemical vapor deposition (CVD) method was used to coat silver wire electrode with CNT, Ag-CNT electrodes performance was studied in present work.

2. Materials and methods

The work presented follows ethical standards.

2.1 *CNT synthesis on silver electrodes surfaces*

CNT were synthesized and deposited on silver wires using floating catalyst chemical vapor deposition (FC-CVD) technique. The experimental setup for this technique was reported by Muataz et al and Amro et al (Muataz et al., 2006; Amro et al., 2014). For synthesized CNT characterization and optimization scanning electron microscopy device (SEM) (JEOL JSM 6460LV) model was used. After optimization of coating parameters transmission electron microscopy (TEM), model (FEI Tecnai G2) was used for CNT characterization.

2.2 *Differential electrolytic potentiometry (DEP)*

An electronic circuit was designed and constructed similar to that reported by Abulkibash et al (Abulkibash et al., 2013). This circuit polarizes electrodes used in DEP using an AC current source. (Fig. 2) shows a sketch of DEP setup. It shows tip of microliter injector in addition to a pair of electrodes accommodated in a small cell. Precise volumes are delivered to the cell using microliter injector designed and built for this purpose (Fig. 2). "Lab View" software was used to monitor the output potential and ac source current.

2.3 *Application of ac-DEP for redox microtitration of KTZ using gold and Ag-CNT electrodes*

Pair a properly cleaned identical gold wires with dimensions (0.17 mm diameter and 20 mm length). After cleaning gold wires with aqua regia they were rinsed with deionized water. Ce(NH4)(SO4)4.2H2O

ISSN (Online): 2789-5289 AJHAS

(BDH)was used for preparation of 0.10 M Ce (IV) solution in 0.5 M H2SO4 . A solution of 0.05 M of pure KTZ was prepared in 0.05M H2SO4. Commercially available KTZ Nizoral® tablets were used in present work, after grinding Nizoral® tablets, amount equal to 200 mg KTZ powder was prepared by dissolving it in 0.05M H2SO4. supporting electrolyte was prepared using conc. H2SO4 (Fisher Scientific) diluted to 5% v/v. Ce (IV) was used as titrant for KTZ microtitration. Ac-DEP technique was used to locate titration endpoint using both Ag-CNT and Au electrodes.

2.4 ac-DEP non aqueous microtitration of KTZ

0.1M HClO4 used as titrant prepared from 72% HClO4 (Fluka) mixed with glacial acetic acid (8.5mL in 500mL), then 30 mL was added to the solution and diluted to 1000 mL with glacial acetic acid. ethyl methyl ketone (2- butanone) (Fluka) was used as solvent for KTZ in non-aqueous titration. ethyl methyl ketone (2-butanone) was used as supporting electrolyte. antimony and Ag-CNT were used as indicating electrodes.

Standard method for KTZ analysis is based on potentiometric titration of KTZ dissolved in a mixture of anhydrous acetic acid and methyl ethyl ketone versus perchloric acid (British pharmacopoeia, 2007).

3. RESULTS AND DISCUSSION

3.1 *Characterization of CNT coated silver electrodes*

The floating catalyst chemical vapor deposition (FC-CVD) was used to synthesize CNTs at the silver wires surface. The optimum parameters for CNT growth on silver electrodes are as follow: C2H2 to H2 gas flow rate ratio is 75:25 mL/minute, reaction temperature is 700°C, reaction time is 15 minutes, and the best electrode position in the reactor in the front 10 cm of the quartz tube. Fig. 3 and fig.4 show SEM and TEM images of CNT coating silver electrode surface respectively.

3.2 *Microtitration of KTZ in aqueous medium using ac-DEP*

Ce (IV) was used as titrant for ac-DEP microtitration of KTZ with gold electrodes as indicating electrodes. Reaction between Ce (IV) and KTZ is oxidation – reduction. Titration curves (Fig. 5a, b) indicated that stoichiometric ratio between Ce (IV) and KTZ is 4:1. This ration is not affected by the concentration of supporting electrolyte.

(Fig. 5c) showed titration curve of KTZ 200 mg tablets which is commercially available with brand name Nizoral ®, which have been grinded then dissolved in acidified water before titration versus Ce (IV) titrant.

When Ag-CNT electrodes were used as indicating electrodes in micro titration of KTZ with Ce (IV) using ac-DEP two peaks are formed, the first one at 1:1 stoichiometric ration and the second one at 3:1 as shown in (Fig. 6a, b).

(Fig. 6c) showed the titration curve of Nizoral® sample which is almost the same as standard KTZ samples titration curves; furthermore, it showed remarkable accuracy and precession compared to official method of KTZ analysis (Table 1).

3.3 *Microtitration of KTZ by ac-DEP in Non-Aqueous medium*

Perchloric acid (HClO4) was used as a standard titrant in non-aqueous acid – base microtitration of KTZ by ac-DEP. The stoichiometric ratio According to traditional method between HClO4 and KTZ is 2:1.

(Fig. 7a, b) showed KTZ ac-DEP microtitration curves using antimony electrodes; table 1 shows a good presession of the method. According to (Fig. 7a, b) different sample volumes of 0.01M KTZ were studied. (Fig. 6c) shoed microtitration curve of 5.0µL 0.01M Nizoral® 200 mg using the same conditions of standard KTZ.

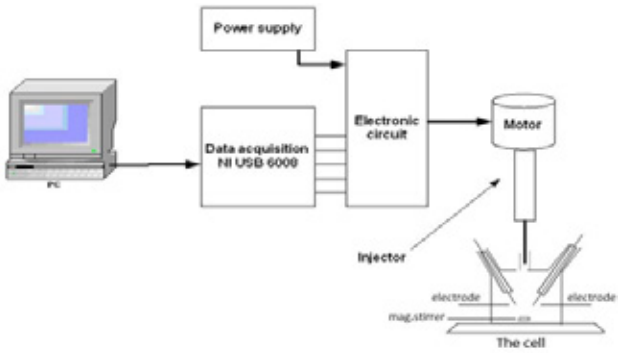

Fig. 2 DEP system block diagram

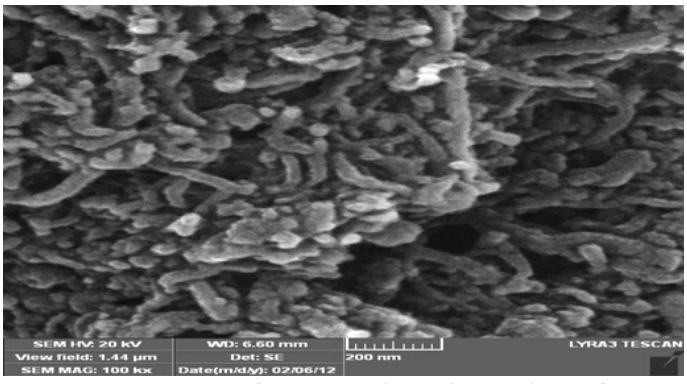

Fig. 3 SEM image of CNT on silver electrode surface

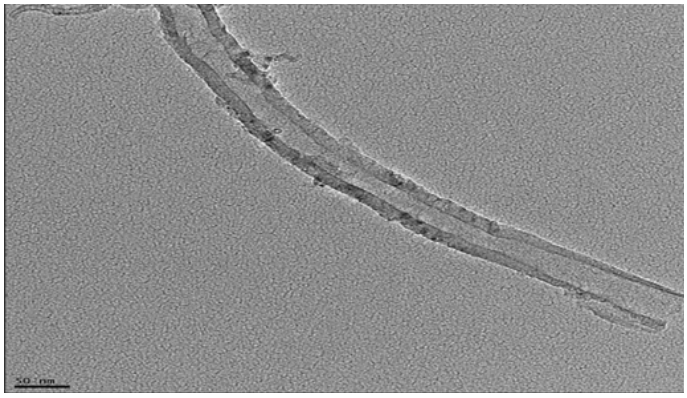

Fig. 4 TEM image of CNT which has been grow on silver wire by CVD

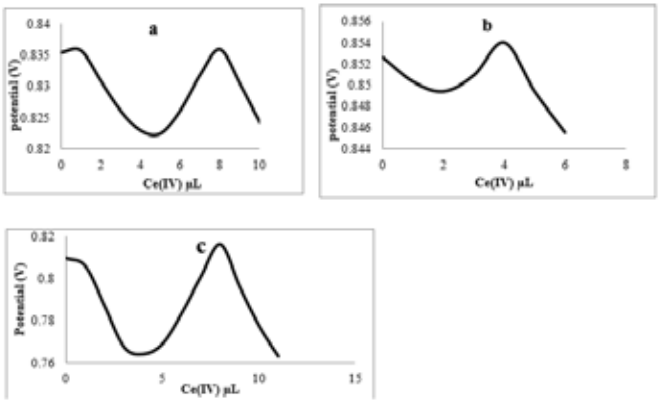

Fig. 5 Ce (IV) 0.1M vs. standard KTZ 0.05M (a) 4.0µL and (b) 2.0 µL (c) KTZ (Nizoral ® tablets 200 mg) 0.04M 5.0µL Gold electrode ac -DEP 5% bias

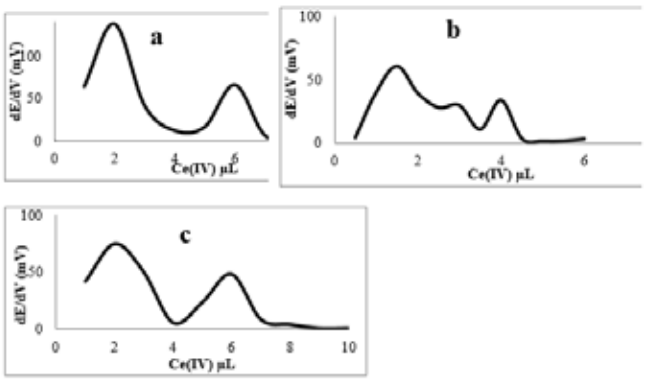

Fig. 6 Ce (IV) 0.1M vs. standard KTZ 0.05M (a) 4.0µL and (b) 2.0 µL (c) KTZ (Nizoral ® tablets 200 mg) 0.04M 5.0µL Ag-CNT electrode ac -DEP 5% bias

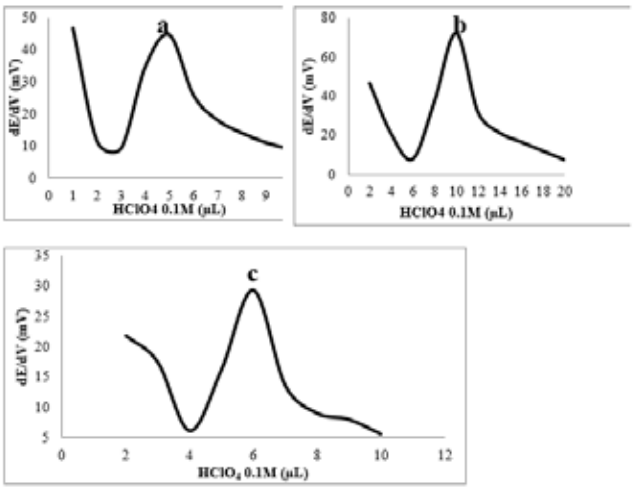

Fig. 7 HClO4 (0.1M) vs. standard KTZ (a) 25µL (b) 50µL 0.01M (c) 30µL Nizoral® 0.01M (non-aqueous) ac -DEP 5 % bias Antimony electrode

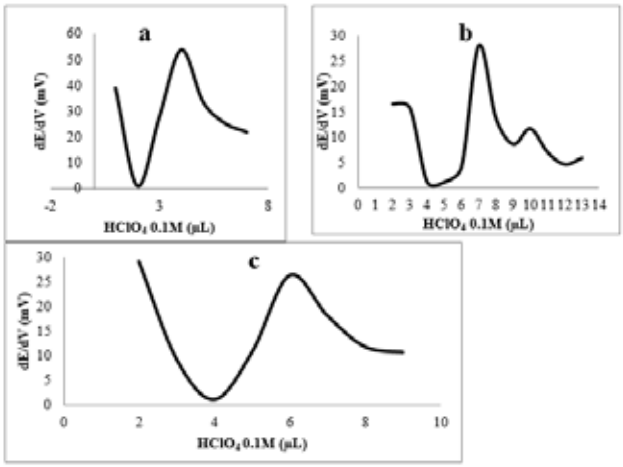

Fig. 8 HClO4 (0.1M) vs. standard KTZ (a) 25µL (b) 50µL 0.01M (c) 30µL Nizoral® 0.01M (non-aqueous) ac -DEP 5 % bias Ag-CNT electrode

Table 1 exhibits a five replicates statistical comparison for KTZ quantitation methods at different medium, according to the table a big difference in sample quantity reaches a thousand-fold between standard official method and the ac-DEP method. Although there is a huge difference in the quantity of the samples, but the recovery and RSD values showed no significant difference in accuracy and precession between them. Usually, decreasing sample volume and mass, increases relative error, but table 1 shows no significant difference in recovery and RSD between studied methods, although the differences between analytes masses reach a thousand-fold between the official method and the developed method. The reason behind this high performance of microtitration using DEP method comes from the accuracy of developed micro liter injector used in this study and the sensitivity of DEP electrodes especially Ag-CNT electrodes. According to table 1 Ag-CNT electrode showed a better accuracy than gold electrode for KTZ microtitration and comparable precession.

Table 1
A Comparison in accuracy and precession for KTZ analysis by ac-DEP in aqueous and non – aqueous medium

Method	Sample	Sample mass (mg)	Recovery %	RSD	Standard deviation
Official method*	Standard KTZ	100	99.1	2.04	2.021
ac-DEP aqueous gold electrode	Standard KTZ	0.106	101.5	1.61	0.002
ac-DEP aqueous Ag-CNT electrode	Standard KTZ	0.106	99.8	4.99	0.005
Official method*	Nizoral® tablets	100	99.2	1.48	1.461
ac-DEP aqueous gold electrode	Nizoral® tablets	0.106	101	5.16	0.006
ac-DEP aqueous Ag-CNT electrode	Nizoral® tablets	0.106	99.5	2.75	0.003
ac-DEP non-aqueous Antimony electrode	Standard KTZ	0.133	99.2	1.80	0.0025
ac-DEP non-aqueous Antimony electrode	Nizoral® tablets	0.159	98.0	2.80	0.004
ac-DEP non-aqueous Ag-CNT electrode	Standard KTZ	0.106	101	1.36	0.001
ac-DEP non-aqueous Ag-CNT electrode	Nizoral® tablets	0.159	99.7	4.64	0.007

*British pharmacopeia

4. CONCLUSIONS

Differential electrolytic potentiometry Microtitration of KTZ exhibited high performance regarding sharp endpoints, high accuracy and precession compared to the official method. Silver electrodes coated with CNT showed comparable recovery and RSD, in addition to sharp endpoints for both aqueous and non-aqueous microtitration of KTZ. Microtitrimetry by DEP using CNT modified silver electrodes is highly recommended for KTZ assay because its green analytical method consumes small amounts of chemicals with high performance.

Acknowledgments

This study was approved by the Deanship of Scientific Research, Al-Ahliyya Amman University.

References

Abdel-Gawad F.M. (1997). Investigation of ketoconazole-iron (III) complex and its spectrophotometric determination in pharmaceutical preparations, Farmaco 52,119–122.

Abdennabi A. (1979). differential electrolytic potentiometric titrimetry in non-aqueous media, PhD thesis, Collage of science, Exeter university, UK

Abulkibash A., AlAbsi M., Amro A.N. (2013). Microtitrimetry by Controlled Current Potentiometric Titration, Journal Analytical Chemistry, 68(1), 57–60.

Ajayan P.M., (1999). Nanotubes from Carbon, Chemical Reviews, 99(7), 1787–1800.

Amro A.N., Abulkibash A., Atieh M.A., (2014). Carbon Nanotubes as Nanosensor for Differential Electrolytic Micropotentiometry, American Journal of Analytical Chemistry, 5(13), 879–890

Andrews F.A., Peterson L.R., Beggs W.H., Crankshaw D., Sarosi G.A., (1981). Liquid chromatographic assay of ketoconazole, Antimicrobial Agents Chemotherapy, 19(1), 110–113.

Arranz P., Arranz A., Moreda J.M., Cid A., Arranz J.F. (2003). Stripping voltammetric and polarographic techniques for the determination of anti-fungal ketoconazole on the mercury electrode, Journal of Pharmaceutical and Biomedical Analysis, 33(4), 589–596.

Bishop E. (1956). Ultra micro potentiometric titrimetric analysis differential electrolytic potentiometry in redox systems, Microchimca Acta, 44, 619–629.

Bishop E. (1958). differential electrolytic potentiometry. Part II. Precision and accuracy of applications to redox titrimetry, Analyst, 83, 212–222.

British pharmacopoeia Volume I & II monographs: Medicinal and pharmaceutical substances, Ketoconazole (2007).

Chen Y.L., Felder L., Jiang X., Naidong W. (2002). Determination of ketoconazole in human plasma by high-performance liquid chromatography–tandem mass spectrometry, Journal of Chromatography B, 774(1), 67–78.

Dantas A.N., De Souza D., de Lima J.E., de Lima-Neto P., Correia A.N. (2010). Voltammetric determination of ketoconazole using a polished silver solid amalgam electrode, Electrochimica Acta, 55(28), 9083–9089.

El Ries M.A., Abdel Ghany M.F., Hussin L.A., El-Anwar F.M., Mohamed A.M. (2013). Voltammetric

behavior of ketoconazole and its determination in cosmetic preparation using a b-cyclodextrin modified glassy carbon electrode, Bulletin Faculty of Pharmacy Cairo University, 51, 49–55.

Farhadi K., Maleki R. (2001) A New Spectrophotometric Method for the Determination of Ketoconazole Based on the Oxidation Reactions, Analytical Science, 17, i867–870.

Fraihat S. and Bahgat K. (2014). Spectrophotometric Methods for the Determination of Ketoconazole in Pharmaceutical Dosage Forms, Tropical Journal of Pharmaceutical Research 13 (9), 1511-1514

Fraihat S. (2014). A sequential injection system for spectrophotometric determination of ketoconazole, Maejo International Journal of Science and Technology, 8(3), 232-239

Gong K., Yan Y., Zhang M., Su L., Xiong S., Mao L. (2005) Electrochemistry and electroanalytical applications of carbon nanotubes, A Review Analytical Sciences 21(12), 1383–1393.

Heydena Y.V., Nguyet A.N.M., Detaevernier M.R., Massart D.L.,Vercammen J.P. (2002). Simultaneous determination of ketoconazole and formaldehyde in a shampoo: liquid chromatography method development and validation, Journal Chromatography A, 958(1-2), 191–201.

Jalali F., Afshoon A. (2008). Spectrofluorimetric Study and Detection of Ketoconazole in the Presence of ß-cyclodextrin, Journal of Fluorescence, 18, 219–225.

Jang J.W., Lee D.K., Lee C.E., Lee T.J., Lee C.J., Noh S.J. (2002). Metallic conductivity in bamboo-shaped multiwalled carbon nanotubes, Solid State Communications, 122 (11), 619–622.

Khashaba P.Y., El-Shabouri S.R., Emara K.M., Mohamed A.M. (2000). Analysis of some antifungal drugs by spectrophotometric and spectrofluorimetric methods in different pharmaceutical dosage forms, Journal of Pharmaceutical and Biomedical Analysis, 22(2), 363–376.

Merkoc A., Pumera M., Llopis X., P´ erez B., del Valle M., Alegret S. (2005). New Materials for Electrochemical Sensing VI: Carbon Nanotubes, Trends in Analytical Chemistry, 24(29), 826–838.

Muataz A.A., Ahmadun F, Guan C, Mahdi E., Rinaldi A. (2006). Effect of reaction temperature on the production of carbon nanotubes, NANO, 1(3), 251–257.

Nugent J.M., Santhanam K.S.V., Rubio A., Ajayan P.M. (2001). Fast electron transfer kinetics on multiwalled carbon nanotube micro bundle electrodes, Nano Letters, 1(2), 87–91.

Odom T.W., Huang J.L., Kim P., Lieber C.M. (1998). Atomic structure and electronic properties of single-walled carbon nanotubes, Nature, 391, 62–64.

Rane S.S., Padmaja P. (2012). Spectrophotometric method for the determination of ketoconazole based on amplification reactions, Journal Pharmaceutical Analysis, 2(1), 43–47.

Sa´nchez-Delgado R. A., Lazardi K, Rinco´n L, Urbina J.A., Hubert A.J., Noels A.F. (1993). Toward a novel metal-based chemotherapy against tropical diseases. 1. Enhancement of the efficacy of clotrimazole against Trypanosoma cruzi by complexation to ruthenium in RuCl2(clotrimazole)2, Journal of Medicinal Chemistry, 36(14), 2041–2043.

Saleh T.A., AlAqad K.M.M., Rahim A. (2018). Electrochemical sensor for the determination of ketoconazole based on gold nanoparticles modified carbon paste electrode, Journal of Molecular Liquids, 256, 39–48.

Tekleab D., Czerw R., Carroll D.L., Ajayan P.M. (2000). Electronic structure of kinked multiwalled carbon nanotubes, Applied Physics Letters, 76, 3594–3596.

Vertzoni M.V., Reppas C., Archontaki H.A., (2006). Optimization and validation of a high-performance liquid chromatographic method with UV detection for the determination of ketoconazole in canine plasma, Journal Chromatography B, 839(1-2), 62–67

Vojic M.P., Popovic G.V., Sladic D.M., Pendt L., (2005). Protolytic equilibria in homogeneous and heterogeneous systems of ketoconazole and its direct spectrophotometric determination in tablets, Journal of Serbian Chemical Society, 70(1), 67–78.

Wang J., (2005). Carbon-nanotube based electrochemical biosensors, A Review. Electroanalysis, 17(1), 7–14.

Wang K., Wu Y., Chi Z., Shu C., Li L., Wei J., Tao L., Ma P., Ding L., (2016). A highly sensitive LC–MS/MS method for determination of ketoconazole in human plasma: Application to a clinical study of the exposure to KTZ in patients after topical administration, Journal of Pharmaceutical and Biomedical Analysis, 128, 504–509.

Conflict of interests:

The author declares that there is no conflict of interests.

Funding statement:

The experimental part of this work has been done at King Fahd University of petroleum and minerals laboratory

Citing the article:

Amro A.N. (2022). Micro titrimetric determination of ketoconazole in both aqueous and non-aqueous media by differential electrolytic potentiometry using metallic electrodes coated with carbon nanotubes. Al-Balqa Journal for Health and Applied Sciences. 1 (1), 26- 32