Original Article

Electrochemical sensing of Metoprolol using MIP/TiO2 based carbon paste electrode

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Abstract

Metoprolol tartrate is beta blocker prescribed for the treatment of hypertension, angina pectoris and cardiac arrhythmias. The electrochemical oxidation of Metoprolol was checked at different modified carbon paste electrodes in phosphate buffer solution (pH =7) using cyclic voltammetry (CV), Differential pulse voltammetry (DPV) and electrochemical impedance spectroscopy (EIS). CV shows an irreversible oxidation peak between the potential range of 0.4 to 1.8V in the phosphate buffer solution at TiO2/MIP/CPE. The Nyquist plot of TiO2/MIP/CPE gives less charge transfer resistance (Rct) as compared to MIP/CPE due to an increase in the conductivity of the surface because of TiO2 particles. The modified electrode gives trouble-free electron transfer due to the porous nature of the material. The fabricated sensor selectively determines Metoprolol amperometrically in the pharmaceutical sample.

Keywords: Metoprolol tartrate, Electrochemical impedance spectroscopy, Differential pulse voltammetry, Chronoamperometry.

1. INTRODUCTION

Metoprolol (MET) is a selective ß1 receptor blocker used in the treatment of several diseases of the cardiovascular system, especially hypertension, angia pectoris, cardiac arrhythmian and myocardial infarction chemically named [1,2].1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol. It is so sensitive that even a small oral dose of the drug gives sufficient blockade and an overdose of such a b-blocker can lead to severe cardiac problems [3]. Because of the sedative effect of MET, the International Olympic Committee [4] has added this drug to the list of forbidden drugs. Therefore, the development of a simple, rapid, sensitive, and selective analytical method for MET determination in both tablets and biological fluids is highly desirable. Various analytical methods have been described for MET quantification in pharmaceutical dosage forms as well as in biological fluids individually or simultaneously with other drugs. These methods consist of spectrophotometry [5,6], atomic absorption spectroscopy and spectrophotometry [7], capillary electrophoresis [8], flow-injection chemiluminescence [9], and various techniques of chromatographic methods [10].

Molecularly imprinted polymers (MIPs) are biomimetic sensing material which provides molecular recognition for different types of biologically active molecules because of the physical robustness and mechanical and chemical stability of polymeric matrix.[11] MIPs find application in many areas such as liquid chromatography, drug delivery, antibody and receptor mimics, artificial enzymes, determination of drugs, cancer biomarkers, viruses, sensing devices, electrochemical, catalysis, immunoassay and sensor development.

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[11] MIPs have been widely used for the determination of various biologically active moieties and also used for sensor application as a possible alternative for unstable natural receptors.[12]

The TiO2 nanoparticles are an area of interest due to their unique technological properties and applications such as memory devices, sensors, photocatalysis and solar cells. It is widely used as a pigment in paints and shows improved performance in the field of photocatalytic applications for the removal of various organic toxins from air and water. The non-toxic and biocompatible properties of titania find applications in biomedical sciences such as bone tissue engineering as well as in pharmaceutical industries [13]. The preparation of ultrafine titania powders has been investigated using various methods such as sol-gel, hydrothermal, solvothermal, flame combustion, emulsion precipitation, fungus-mediated biosynthesis, etc. In modern nano-science and -technology, the interaction between inorganic nanoparticles and biological structures is one of the most exciting areas of research [14].

An electrochemical measurement essentially uses an electrochemical cell which comprises of two or three-electrode systems i.e. working electrode (WE), reference electrode (RE) and counter electrode (CE). The current and potential range of the electrochemical system can be changed according to the mode of electrochemical operation and the method is based on the enhancement of specificity and selectivity of the sensor. The present work reports the fabrication of an electrochemical sensor for MET based on MIP/ TiO2/CPE carbon paste electrode (CPE). The TiO2/MIP/CPE was used because of high electrochemical reactivity, ease of polishing, low cost and good reproducible surface. The MIP was prepared by bulk polymerisation of methacrylic acid and MET. TiO2/MIP/CPE was used for the electrochemical detection of MET utilizing amperometry.

2. EXPERIMENTAL

2.1. Chemicals and materials

Metoprolol was purchased from Sigma Aldrich. Methacrylic acid (MAA), Ethylene glycol dimethacrylate (EGDMA), azo-bisisobutyronitrile (AIBN), eicosane, graphite powder (particle size <20 micron), Titanium powder, ascorbic acid were purchased from Sigma Aldrich. Dipotassium monohydrogen phosphate, mono-potassium hydrogen phosphate, potassium chloride, urea, glucose, tryptophan, and uric acid were purchased from Merck. Potassium ferrocyanide K4[Fe(CN)6] 4-, potassium ferricyanide K3[Fe(CN)6] 3- and MET tablets were purchased from Fischer Scientific and general medical stores respectively.

2.2. Apparatus and Equipment:-

Electrochemical measurements were done with the help of a three-electrode system. Electrochemical studies including cyclic voltammetry (CV), differential pulse voltammetry (DPV) and Electrochemical impedance studies were carried out using Gamry 1000 potentiostat interfaced with Echem Analyst software. A MIP-modified carbon paste electrode(MIPCPE), Ag-AgCl electrode (Gamry) and Pt wire were used as working, reference and counter electrodes respectively. Morphological characterization was carried out by Scanning electron microscope (SEM) and diffraction studies were performed using XRD. The Absorption spectra of the samples were analyzed by the Shimadzu model UV-1800 spectrophotometer with a quartz cell of 1cm path length. The pH measurements were done using a Toshniwal pH meter.

2.3. Preparation of Metoprolol MIP Particles

The procedure for the synthesis of MIP polymer was as follows: In the 20ml glass template (Metoprolol 1mM), functional monomer (MAA; 4mM), cross-linker (EGDMA; 20mM) and initiator (AIBN; 0.5mM) in chloroform (20 ml) were added. The mixture was purged with nitrogen for 10 min to remove any dissolved oxygen, which would inhibit free radical polymerization. The polymerization was allowed to continue in a water bath at 60 °C for 18 h. After polymerization, a hard polymer monolith was obtained, which was crushed and ground into a fine powder with a mortar and pestle. Soxhlet extraction was performed to remove the template with 70:30 (V/V) methanol: acetic acid overnight. Then, the polymer was washed several times with pure methanol to remove the acetic acid and facilitate drying. The dried polymer was now ready for use.

2.3. Preparation of TiO2 nanoparticle

` Titanium powder (2mg) and 25 ml of 4M hydrochloric acid [HCl] were used as a precursor to obtaining Titanium tetra chloride (TiCl4). TiCl4, 25m ethylene glycol and 10gm of urea were heated at 180 ˚ C for 4 hours which leads to the formation of white ppt of TiO2. The ppt was then washed with acetone and ethanol. The ppt was then dried in the oven at 100 ˚ C for about 15 hours followed by calcination at 500 ˚ C for 2 hours. The calcined powder was utilized for further characterization and electrode modification.

2.4. Electrode preparation

TIO2/MIP/CPE was prepared by mixing 4mg of TiO2, 8mg MIP and 50mg graphite powder using n-eicosane (20mg) as a binder molecule. The resultant carbon paste was filled into a hollow Teflon tube of 10 mm inner diameter. The other end of the Teflon tube was connected to a copper wire for electrical contact. The exposed surface is polished with butter paper before the experiment. After a set of electrochemical impedance measurements, a new surface is exposed by removing a thin layer of carbon paste followed by polishing.

2.5. Real sample analysis

The fabricated TiO2/MIP/CPE quantitatively determined the concentration of MET in the pharmaceutical sample. A pharmaceutical sample solution of Metoprolol (1mM) was prepared by dissolving the proper weight of powdered tablets of the proper weighed amount of MET in a

Phosphate buffer of pH 7. Different dilutions were made by mixing aliquots of sample solution and phosphate buffer for spiking and calculating % recovery.

3. RESULT AND DISCUSSION

3.1. Characterization of TiO2 particle:-

XRD:

The powder XRD method was used for the structural analysis of TiO2 nanoparticles. The diffractograms were recorded in the 2ɵ range of 10-80º. Figure 1 shows representative XRD patterns taken from Sol residues heated at 300º C for 2 h. The XRD result of the TiO2 particle shows crystalline nanoparticles and a diffraction pattern corresponding to the Anatase and Rutile phases of TiO2. The broad lines were comparatively broad representing nano-size crystals. The XRD patterns exhibited diffraction peaks at 25.44º, 36.16º, 47.91º, 52.43º, 55.4º and 63.5˚ indicating TiO2 in the anatase phase with the corresponding (101), (004), (200), (105), (211) and (204) planes respectively. The peaks observed at 69.35º and 75.60 indicated TiO2 in the rutile phase with the corresponding (220) and (224) planes respectively. All observed peaks are in good agreement with the standard spectrum (JCPDS no.: 21-1272 and 21-1276). [15]

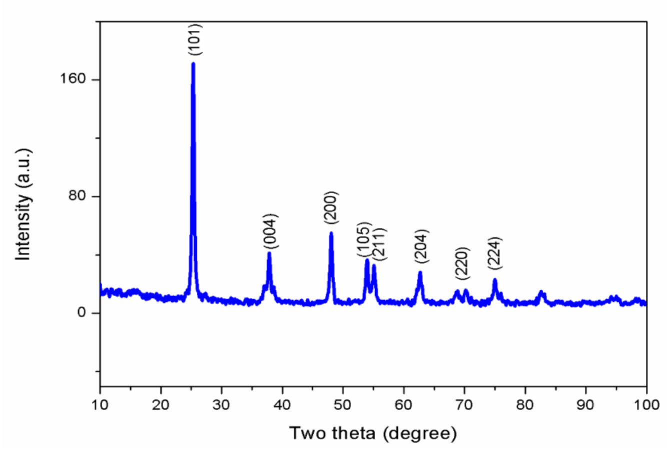

Fig 1. XRD pattern of TiO2 nanoparticle

SEM:

Further structural study of the prepared TiO2 powder was studied using FE-SEM image analysis. Fig. 2 shows the FE-SEM image of synthesized TiO2 powder, which is heated at 500 ºC. From FE-SEM images aggregated spherical TiO2 particle size was obtained at ~25 nm. The FE-SEM images show the high degree of crystallinity of the TiO2 nanoparticles. The particle was found spherical in shape and surface morphology was found homogenous in specific regions. The agglomeration of the particles was seen in the FE-SEM images.

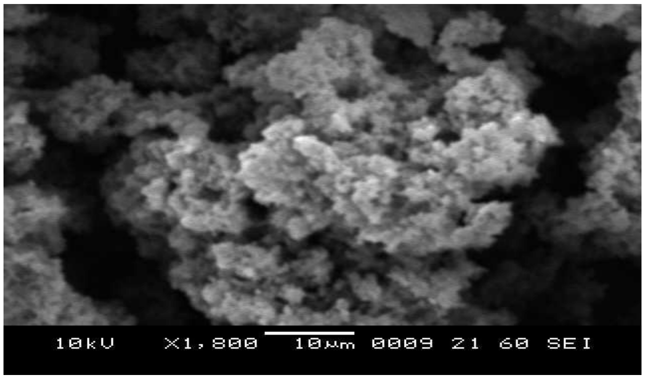

Fig 2. FESEM of TiO2 naoparticle

3.2. Characterization of TiO2/MIP/CPE

A scanning electron microscope (SEM) was used to study the morphology of TiO2/MIP/CPE. As shown in Fig.3 TiO2/MIP/CPE is attributed to the rough and irregular surface with clearly visible pores specific for MET and agglomerated globular structure of Titania particle.

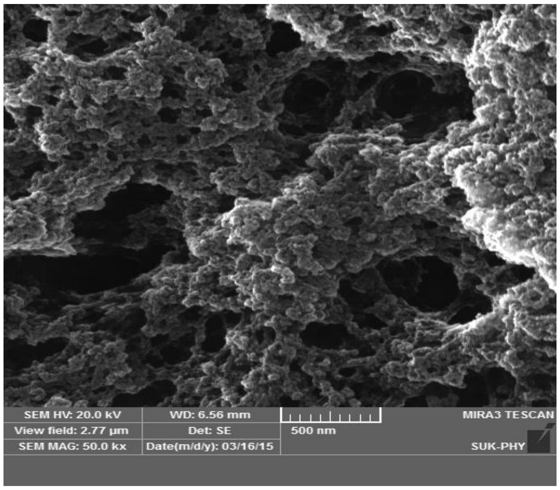

Fig 3. FESEM of TiO2/MIP/CPE

3.3. Electrochemical Characterization by CV and EIS:-

3.3.1. Cyclic Volyammetry (CV):-

The cyclic voltammograms were taken in the phosphate buffer of pH 7 containing 60µM Metoprolol (Fig. 4) showing an electrochemically irreversible peak at 1.45V. The anodic peak current gradually increases from bare CPE to TiO2/MIP/CPE, the result is attributed due to the combined effect of MET-specific pores and the electrical conductivity of TiO2 particles.

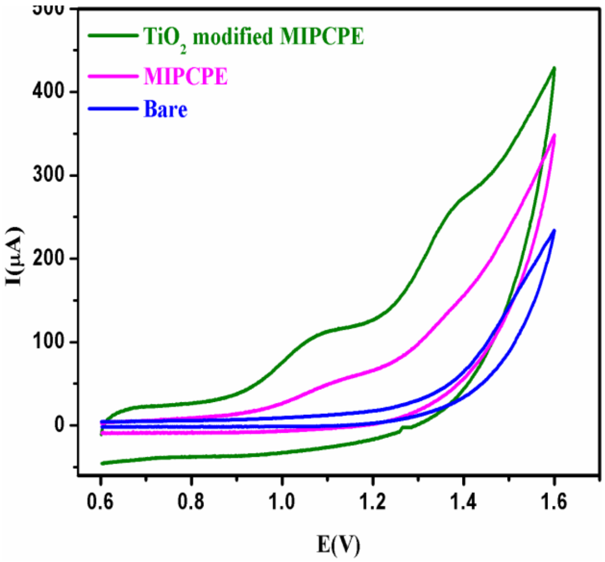

Fig 4:- CV of Bare, MIPCPE and TiO2/MIP/CPE in phosphate buffer of pH 7 containing 60µM MET

3.3.2. EIS:-

EIS is an efficient technique to study the electrode-electrolyte interface properties of the TiO2/MIP/CPE. The impedance spectra of TiO2/MIP/CPE, TiO2/CPE, MIP/CPE and bare CPE were recorded (Figure 5) in 0.1 M KCl containing 5 mM [Fe(CN)6]3_/4_ as redox probe with small excitation amplitude of 10 mV peak to peak over the frequency range of 100 kHz to 10 MHz. From the Nyquist plots, it is clear that the MIPCPE shows a semicircle with a larger diameter with a higher charge transfer resistance (Rct) value of 14.9 kΩ. However, the value of Rct for TiO2/MIP/CPE was significantly reduced to 7.8 kΩ as a consequence of conducting nature of the Titania particle.

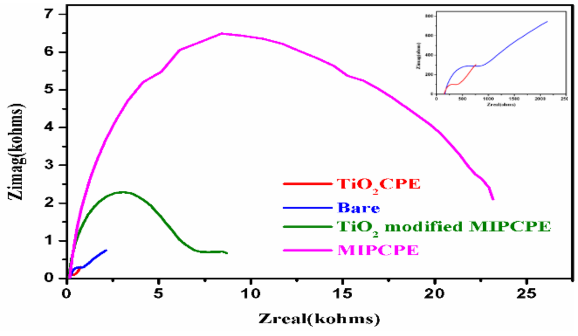

Fig 5:- Nyquist plot of different electrode using 5mM [Fe(CN)6]3-/4- system

3.4. Electrochemical determination of Metoprolol by Chronoamperometry:-

The calibration curve of the sensor is represented in Fig. 6. As can be seen, the signal of the sensor changes sharply, when increasing Metoprolol concentration from 10µM to 120 µM. The dynamic linear range established based upon the first sharply ascending line in the original calibration curve (10µM to 120 µM) was chosen as the linear range of the sensor for Metoprolol determination purposes. Also, the detection limit of Metoprolol using the developed TiO2/MIP/CPE was found to be 5µM.

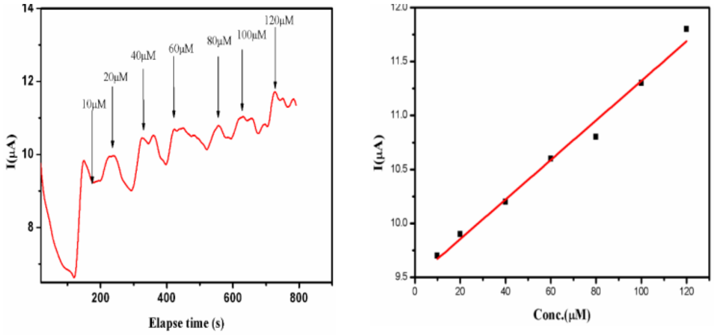

Fig 6:- Chronoamperometric response of TiO2/MIP/CPE for various concentration of MET [A] (10 µM to 120 µM) in 0.1M phosphate buffer at applied potential of 1.4V with calibration curve (B)

3.5. Selectivity studies

The electro-oxidation of MET at TiO2/MIP/CPE was examined under the influence of common interferents such as tryptophan (TRY), Glucose (GLU), urea, ascorbic acid (AA) and uric acid (UA) to evaluate the selectivity of the sensor. Selectivity studies were performed using an equal concentration of both MET and interferents (20µM) with the help of Chronoamperometry. To a definite concentration of MET, interferents of the same concentration were successively added at a definite time interval and current responses were analysed amperometrically. Fig. 7 shows the chronoamperometric response on successive additions of 20 µM MET, 20 µM Tryptophan, 20 µM glucose, 20 µM Urea, 20 µM ascorbic acid, 20 µM uric acid and 20 µM MET in PBS (pH 7.0) maintained at 1.45 V operational potential. It was observed that no variation or increase in current on adding interferents, which suggests that only MET is oxidized at the surface of TiO2/MIP/CPE.

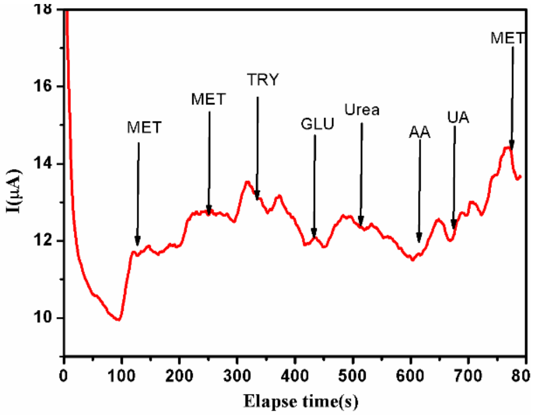

Fig 7. Chronoamperometric curve obtained for TiO2/MIP/CPE in PBS pH 7.0 at a fixed potential of 1.4 V showing effect of interferent species in the presence of 20µM MET

3.6. Real sample analysis

The analytical applicability of TiO2/MIP/CPE was analysed using a pharmaceutical tablet (Metoprolol tartarate). Samples of the tablet were 25 times diluted with PB solution (pH 7.0) and recovery rates were carried out by spiking different aliquots of MET in the same solution. Table 1. Shows the result obtained for analysis of a pharmaceutical sample. The proposed method was applied for MET measurement with an acceptable recovery rate ranging from 96% to 102%.

Table 1. Determination of MET content in Metoptolol tartarate tablet.

Sr. No.	Sample	Conc. Added (µM)	Conc. Found (µM)	% Recovery (%R)	Avg. %R
1	Metoprolol tartarate tablet	1	0.96	96%	99 %
2		5	5.10	102%	
3		10	9.99	99%	

4. CONCLUSION

Chronoamperometric determination of MET has been reported by using a binary mixture of catalytic TiO2 and selective MIP of MET. The electrochemical behaviour of MET at TiO2/MIP/CPE was studied by CV and EIS. The fabricated sensor shows better selectivity and electrocatalytic activity for MET under optimized conditions. Electrochemical impedance studies show less charge transfer resistance for TiO2/MIP/CPE. TiO2/MIP/CPE selectively analysed MET in presence of common interferents. The proposed sensor was successfully employed for the determination of MET in a pharmaceutical sample with an acceptable recovery percentage.

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