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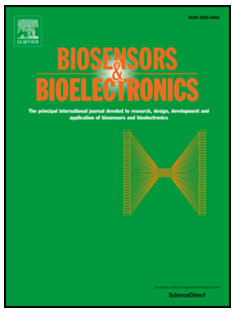

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Sharad S. Upadhyay, Nayan S. Gadhari, Ashwini K. Srivastava

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CREDIT AUTHORSHIP STATEMENT

Sharad S. Upadhyay: Conceptualization, Investigation, Writing-original draft preparation

Nayan S. Gadhari: Resources

Ashwini K. Srivastava: Conceptualization, Supervision, Project administration, Methodology, Writing - Review & Editing

Biomimetic sensor for Ethambutol employing β-Cyclodextrin mediated chiral copper metal organic framework and carbon nanofibers modified glassy carbon electrode

Sharad S. Upadhyay, Nayan S. Gadhari, Ashwini K. Srivastava*

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (East), Mumbai-400 098, India.

* Corresponding Author. Tel.: +91 22 26543570

Email: aksrivastava@chem.mu.ac.in (A.K. Srivastava)

Abstract:

Stereochemical configuration of the drug is responsible for racemic switch with enantiomers in presence of chiral environment for human beings. Therefore, its determination in racemic and pharmaceutical samples becomes a challenge. Addressing this issue, an enantioselective electrochemical biomimetic sensor for discrimination of isomers of ethambutol (ETB) employing square wave voltammetry (SWV) is reported for the first time. For this purpose, a chiral host, β-Cyclodextrin based copper metal organic framework (CD-CuMOF) was synthesised and used for chelate complexation of ETB isomers (SS-ETB/RR-ETB). A glassy carbon electrode (GCE) is chemically modified using CD-CuMOF and carbon nanofibers (CNF) composite material to construct a sensor in the form of (CD-CuMOF-CNF-GCE). The behaviour of CD-CuMOF for ETB isomers on GCE is postulated to be an artificial enzyme model (AEM) as it mimics the catalytic activity similar to enzyme alcohol dehydrogenase for ETB. The biosensor exhibits excellent peak potential difference (ΔEp (SS-RR) = 108 mV) between ETB isomers using SWV showing a clear distinction in the racemic mixture. It showed a linear response in the range of 1.0×10^{-7} to 1×10^{-4} M and 5.0×10^{-7} to 2.5×10^{-4} M with low detection limit of 3.10×10^{-8} M and 8.52×10^{-8} M for RR-ETB and SS-ETB isomers respectively. The sensor was applied for the estimation of ETB isomers in racemic mixture and real samples viz., blood, urine and pharmaceutical. The CD-CuMOF is a low-cost material with higher stability than enzyme and offers an advantage for sensing and catalysis in future.

Keywords: Chiral metal organic frameworks; Ethambutol isomers; Chemically modified chiral electrode; artificial enzyme model; Square wave voltammetry.

1. Introduction

Stereochemistry of any drug molecule must be carefully considered in fields of pharmaceutical, clinical and medicinal sciences. Therefore, enantiomers of all chiral bioactive molecules must be separated and tested (Guebitz and Schmid, 2004). To achieve enantiomer discrimination of any analyte, chiral environment is necessary which is provided by a chiral ligand. To be effective, a chiral ligand must fulfil several requirements namely; 1) It must be stereoselective, 2) able to form "tight fit" inclusion complex and 3) exhibit spontaneous and fast complexation kinetics (Zhu and Scriba, 2016). Natural and derivatised cyclodextrins (Dong et al., 2017; Upadhyay and Srivastava, 2019) are very popular class of chiral ligands due to their, hydrophobic cavity, ability to form complex, easy functionalization and availability at cheaper cost. In this context, β-cyclodextrin (CD) has been reported as an ideal chiral host having thirty-five chiral sites on seven glucose units for accommodation of guest biomolecule (Li et al., 2017; Upadhyay et al., 2019).

Metal organic frameworks are one/two/three dimensional porous materials which consist of an extended network of metal ions or atoms coordinated to multi-dentate ligands (organic molecules) (Gillivray, 2010). Chiral metal-organic frameworks (MOFs) show great potential in enantiomer separation and in the area of asymmetric catalysis (Hartlieb et al., 2016; Padmanaban et al., 2011). However, the usage of chiral MOFs on electrochemical discrimination of enantiomers has been rarely reported (Deng et al., 2017; Wang et al., 2014).

To imitate the enzyme activity any artificial enzyme model (AEM) must possess hydrophobic cavity as a binding site for substrate and also effective site for catalytic activity (Murakami et al., 1996). Literature reports suggests that natural (Upadhyay and Srivastava, 2019; Bender and Komiyama, 1978) and modified CD are widely used as AEM (Tabushi and Kodera, 1987). Here, we report CD-CuMOF as an AEM for ETB enantiomers in the present work which mimic the role similar to alcohol dehydrogenase.

Herein, it is shown that CD can interact with carbon nanofibers (CNF) through non-specific electrostatic interactions. These interactions affect the physicochemical properties of the CNF, making their suspension more hydrophilic and better dispersed, which is essential for reproducible electrode modification (Szot-Karpinska et al., 2019).

Stereochemical configuration in ETB produces three enantiomorphs viz., SS-ETB (active), RR-ETB (toxic) and RS-ETB (inactive). SS-ETB is 12 times more potent than RR-

ETB and RS-ETB (Thomas et al., 1961). SS-ETB has anti-bacterial activity whereas RR isomer may cause optical neuritis which can lead to blindness. ETB possess four coordinating sites and forms chelate complexes with bivalent metal ions (Cu^{2+}/Ni^{2+}/Co^{2+}/Zn^{2+}) (Bhattacharya et al., 1990). There is a broader interest in copper (II) complexes with chelating organic ligands because it often enhances the biological activity (Santini et al., 2014). If such a Cu-ETB chelate is incorporated into CD, the coordination geometry of the ligand is expected to be conserved even if the metal ion is knocked out and the cavity size of the embedded chelate shall remain specific to Cu^{2+}. Inside the cavity, the complexed drug will be unaffected by physical and chemical reactions happening outside. Therefore, considering all these factors, we selected a cyclodextrin-copper MOF and CNF (CD-CuMOF-CNF) for the discrimination RR-ETB and SS-ETB employing voltammetric techniques in the present work.

A very few methods have been reported for separation of ETB enantiomers using gas-liquid chromatography (Kim et al., 1981), HPLC (Blessington and Beiraghi, 1990) and HPLC coupled CD detector (Blessington et al., 1992). Copper (II) complexes have been used for the determination of ETB in pharmaceutical formulations using UV spectroscopy (Faria et al., 2011), capillary zone electrophoresis (Faria et al., 2008) and in potentiometric sensors (Gupta et al., 2003).

To date, there are only a few electrochemical methods previously reported for ETB determination without any discrimination of isomers (Cheemalapati et al., 2014; Ngece et al., 2011). Therefore, in this context, we describe for the first time simple, rapid and enantioselective voltammetric method for discrimination of ETB enantiomers.

In the present work, a CD-CuMOF-CNF-GCE electrode system has been developed and applied for the efficient stereoselective discrimination of SS/RR-ETB isomers employing square wave voltammetry (SWV). ETB enantiomers was discriminated based on difference in complexation ability employing voltammetry. Once CD-CuMOF was anchored on the surface CNF, the working electrode simultaneously inherited three things: 1) providing chiral environment for recognition 2) as a complexing agent and 3) the excellent electrical conductivity of CNF. Also, CD-CuMOF on GCE acts as an artificial enzyme.

2. Experimental

2.1. Choice of materials and instrumentation

SS-ETB and RR-ETB (Cipla Ltd. (India)), β-CD, CNF (99.99%) (Aldrich, India), Copper nitrate trihydrate (Cu $(NO_3)_2.3H_2O$), benzene-1,3,5-tricarboxylate (BTC), and N, N-dimethylformamide (DMF) used in this work were purchased from S. D. Fine, India. A stock solution of 1.25 x 10^{-3} M of ETB isomers was prepared in methanol. Phosphate buffer (PBS) of pH 7.0 (0.1 M) was used as supporting electrolyte for overall analysis. The working standard solutions of different concentrations were prepared by diluting appropriate quantity of stock solution to desired volume by using 0.1 M PBS buffer (pH 7.0).

Electrochemical measurements such as SWV, cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) were performed using an Autolab PGSTAT302 N (The Netherland) equipped with USB electrochemical interface using NOVA software (version 1.11.2). A conventional three electrode system employing reference (Ag/AgCl), auxillary (Pt wire) and working electrodes was used. ELICO LI 120 (India) pH meter combined with glass electrode was used for pH measurements. XRD (Shimadzu 7000S equipped with CuK_α radiation (λ= 0.154 nm) Kyoto, Japan, SEM (FEI Quanta-200, USA) and EDX were performed on FEI INSPECT F50 (USA). HPLC (Waters 2695, USA) was used for the comparison of the proposed method. All the experiments were performed at room temperature of 298 ± 2 K.

2.2. Treatment and determination of real samples

The pharmaceutical formulations, Myambutol (400 mg/tablet) and Albutol (200 mg/ tablet) were crushed then dissolved in 100 ml of double distilled water, sonicated and filtered through Whatman paper no.1. An aliquot of the filtrate was then diluted to 25 ml with 0.1 M PBS buffer and used for analysis. The quantitative determination of drugs in real samples was carried out by standard addition method where a standard solution of drug was spiked in to the real sample solution. The blood serum and urine samples of healthy volunteers were obtained from local pathology laboratories with their consent.

2.3. Electrochemical recognition of ETB isomers

The CV experiments were carried out by sweeping potential from 0.7 to 1.3 V. The EIS were carried out in the frequency range 10^{-2} to 10^{6} Hz by using 5mM $[Fe(CN)_6]^{-3/-4}$system. Stock solution (1.25 x10^{-3}M) of ETB was taken in to 25 mL volumetric flask and diluted up to the mark with 0.1 M PBS buffer. The solution was then poured in to the electrochemical cell where the measurements were carried out.

2.4. Fabrication of chiral electrochemical sensor (CD-CuMOF-CNF-GCE)

Prior to fabrication of CD-CuMOF-CNF-GCE, the surface of GCE was polished with aqueous slurry of alumina powder (α-Al_2O_3, 1.0 mm and 0.3 mm) until a mirror like finish was obtained. Then the electrode was washed with distilled water followed by drying under IR lamp. Afterwards, 2 mg of CD-CuMOF and 2 mg of CNF were dispersed in 2 mL DMF and the resulting mixture was ultrasonicated for 15 min till a homogenous dispersion was obtained. 10μL of this mixture was then dropped onto the surface of freshly polished GCE and dried under IR lamp for 10 min, which was used as CD-CuMOF-CNF-GCE. In the similar way CD-CuMOF-GCE was also constructed.

3. Results and discussion

3.1. SEM, EDX and XRD Analysis

SEM analysis of CD shows that it has irregular shape with nanocavities (Fig. S1 (A & B)) which entrap the ETB isomers. The presence of CNF on CD is clearly visible (Fig. S1 (C & D)). The CuMOF nanocubes have been uniformly decorated over the CD-CNF surface (Fig. S1 (E & F)). EDX analysis CD-CuMOF-CNF confirms the presence of elements such as copper, carbon and oxygen (Fig. S1(G). The XRD patterns of CD, CNF, Cu-MOF and CD-CuMOF-CNF show characteristic peaks which support the synthesis of chiral nanocomposite (Fig. S2 (A)). The figures and detail discussion of SEM and XRD is given in S3.1. The pH and electrode characterization are discussed in supporting information S3.2 and S3.3 respectively.

3.2. Chiral discrimination of RR-ETB and SS-ETB employing square wave voltammetry

The chiral discrimination of ETB was based on difference in peak potential of isomers. The square wave voltammograms of 5.32 x 10^{-5} M RR-ETB and SS-ETB at the bare GCE are completely overlapped (ΔE_p= 0.0 mV) with each other as visible from Fig. 1(A), which indicates the absence of recognition ability of GCE. It can be easily ascertained that due to the absence of asymmetric centre, enantiorecognition cannot be achieved successfully on GCE. However, by using CD-CuMOF-GCE discernible differences in anodic oxidation potential (E_p) and peak current (I_p) of both enantiomers are observed as shown in Fig. 1 (B). However, the difference in peak potential (ΔE_p= 46 mV) obtained by CD-CuMOF-GCE was smaller due to which enantiomers detection was not satisfactory. This problem could be overcome by using CD-CuMOF-CNF as a working electrode where CD acts as a chiral selector, CuMOF for support of chelate complex to CD and CNF as a signal enhancer in the

form of CD-CuMOF-CNF-GCE. Using this electrode, greater enantioselectivity could be achieved for RR-ETB and SS-ETB with a significant difference in anodic peak potentials (ΔE_p= 108 mV) and peak currents as observed from Fig. 1 (C). This preferential treatment of CD-CuMOF towards SS-ETB is possible due to synergistic effect of CD, CuMOF and CNF composite material. Because ETB is highly stereospecific, the -OH and -NH- probably provided the platform for stronger H-bonding with CD-CuMOF (Wilkinson et al., 1962; Wilkinson et al., 1961). The higher value of stability constant (K) and more negative Gibbs free energy (ΔG) for SS-ETB (Table 1) in comparison to RR-ETB obtained from complexation studies confirm excellent enantioselective capability of the system. Scheme 1(A) illustrates the mechanism of complexation. The details of complexation study are given in S3.4.

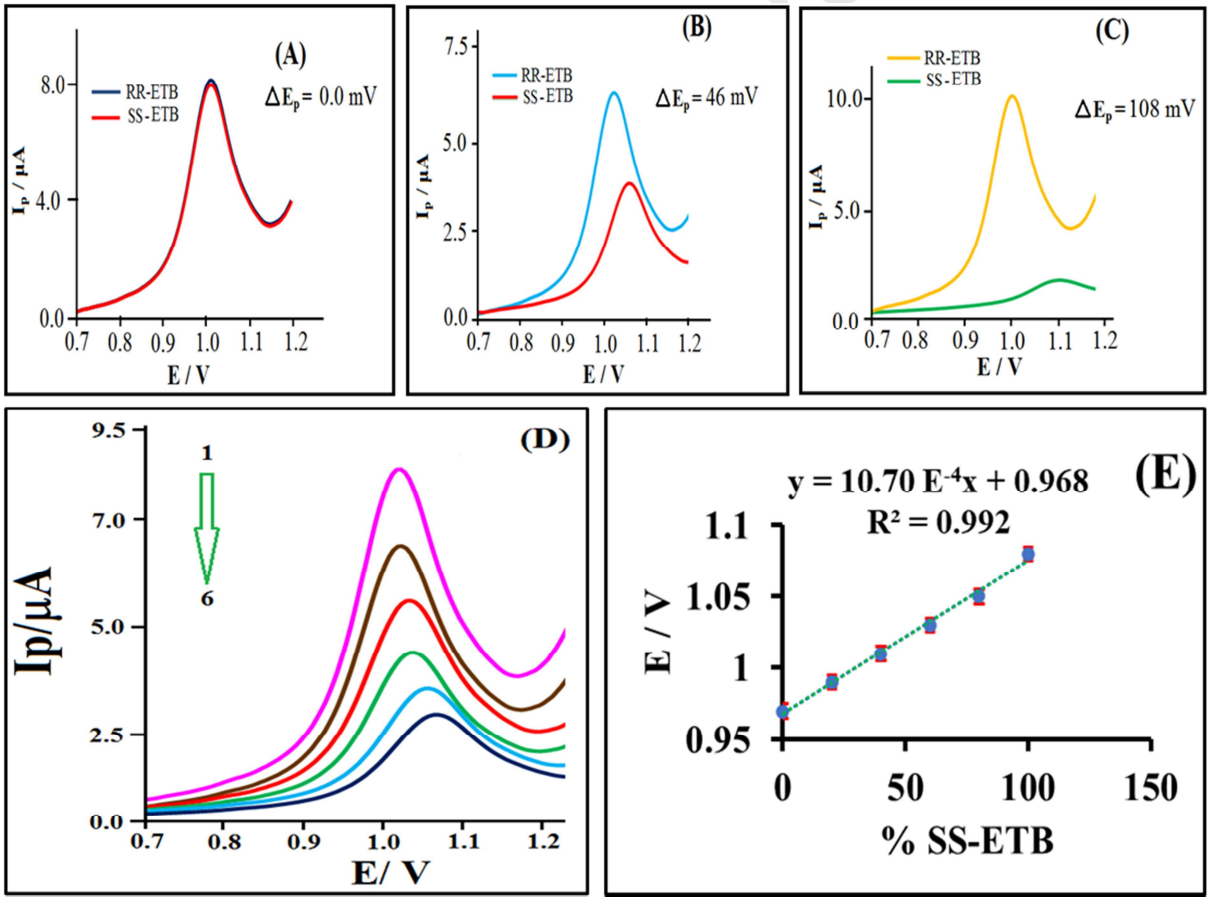
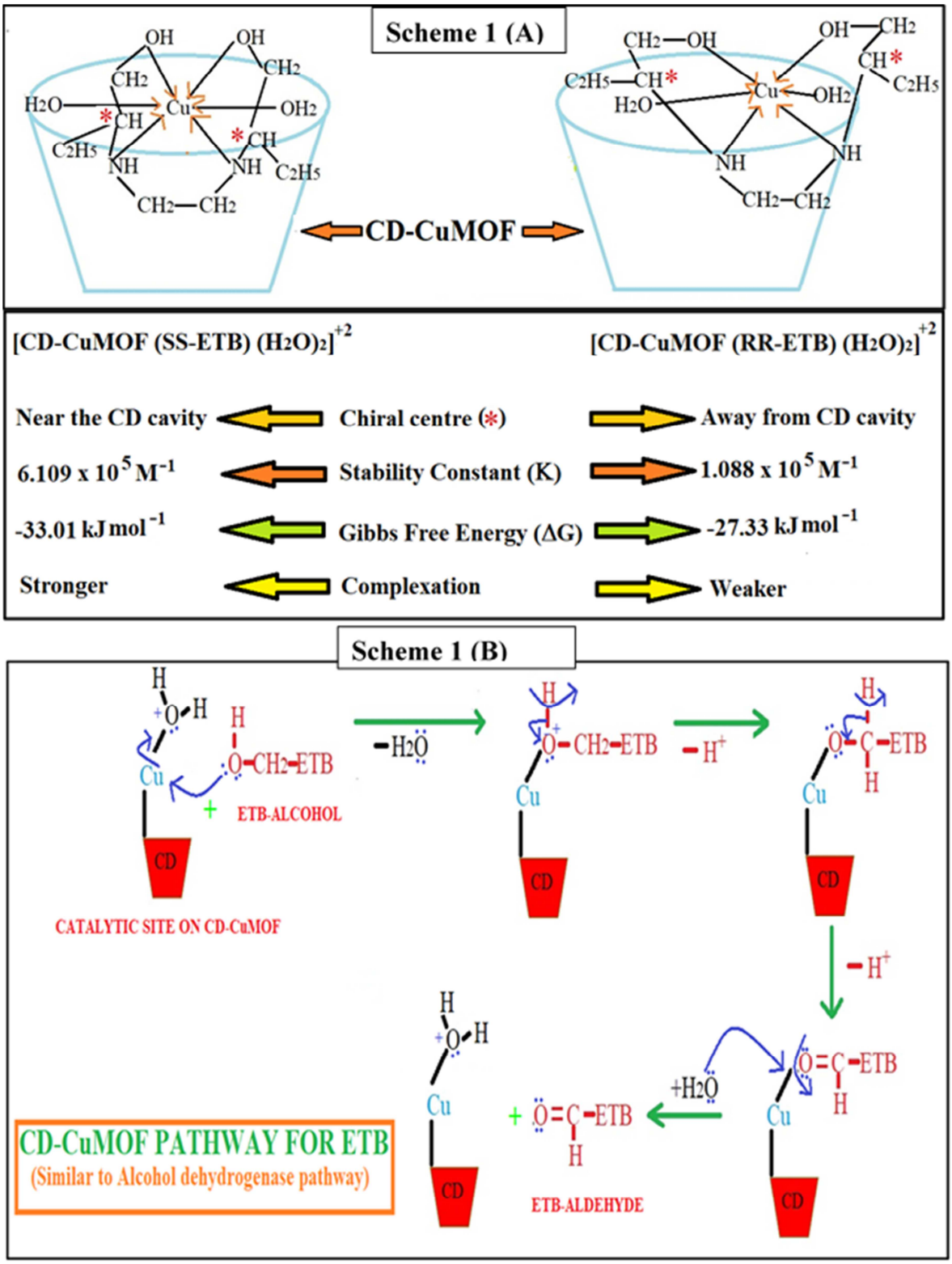


Fig.1. Square wave voltammograms of 5.32 x 10^{-5} M SS-ETB and RR-ETB at **(A)** GCE **(B)** CD-CuMOF-GCE and **(C)** CD-CuMOF-CNF-GCE in PBS buffer (pH 7.0), **(D)** Voltammograms of different SS-ETB% (1-6) 0, 20, 40, 60, 80 and 100% respectively of 1

μM SS-ETB on CD-CuMOF-CNF-GCE; **(E)** Error bar for relationship between E/V and SS-ETB % in the mixture of ETB enantiomers.

3.3. CD-CuMOF as artificial enzyme model for inhibition of ETB isomers

Alcohol dehydrogenase (ADH) is an oxidoreductase enzyme that oxidizes ethanol to acetaldehyde (Cook and Cleland, 1981). Here, we propose similar type of mechanism by using CD-CuMOF as an enzyme mimic for ADH to anti-TB drug ETB. Metabolic transformations of ETB are carried out by ETB-alcoholic functional group (ETB-OH) to ETB-acetaldehyde (ETB-CHO) facilitated by transfer of electrons at CD-CuMOF-GCE on catalytic site of CD-CuMOF similar to ADH (Peets and Buyske, 1964). Two amino groups of ETBs acting as a charge-relay network to help deprotonate the ETB-OH and activate it to be oxidized to the ETB-CHO. Before -OH group enters, a water molecule is initially positioned in the active site, but dissociates when the ETB-OH gets inside it. At the end of the mechanism, water again enters the active site when the oxidized substrate ETB-CHO escapes out. Scheme 1(B) illustrates CD-CuMOF pathway for ETB.



Scheme 1 (A): Mechanism of interaction of complex formed between isomers of ETB and CD-CuMOF and (B): CD-CuMOF pathway for ETB.

3.4. Linearity and Interference studies

Linearity studies for RR-ETB and SS-ETB isomers (Fig.S5. (A & B)) with different concentrations at the CD-CuMOF-CNF-GCE in 0.1 M PBS solution was carried out under optimized conditions (Shi et al., 2017). The peak currents linearly increased with an increase in the concentration, indicating the electrode was sensitive to quantitative determination of both RR-ETB and SS-ETB. The detail description of linearity study has been given in supplementary information S3.5. Under optimal experimental conditions, the interference from selected metal ions and organic compounds was evaluated which gave relative error less than ± 5.0 % at a concentration of 5.2×10^{-5} M of RR-ETB and SS-ETB. The interference studies have been discussed in detail in S3.6.

3.5. Analytical application of enantioselective electrochemical sensor in racemic solution

In the current work, CD-CuMOF-CNF-GCE was used for analysis of SS-ETB in the racemic solution. Varying concentrations of SS-ETB in racemic mixture are shown in Fig. 1 (D), interestingly the anodic oxidation peaks change drastically suggesting recognition of SS in presence of its antipode RR-ETB. Total concentration of racemic mixture was kept constant at 1μM. Enantiomeric percentage of increasing concentration of SS-ETB and peak potential shows linear relationship as observed in Fig. 1 (E).

3.6. Stability and reproducibility of the CD-CuMOF-CNF-GCE

Stability of the CD-CuMOF-CNF-GCE was tested by keeping the electrode in pH 7.0 PBS for 15 days and then the SWVs were recorded and compared with the voltammograms for RR-ETB and SS-ETB (5.32×10^{-5} M) obtained before immersion. The results indicated that the I_p decreased very slightly for CD-CuMOF-CNF-GCE, which indicates that it has good stability. The stability of CD-CuMOF-CNF-GCE over time was checked during a period of 4 months. A very small change in the voltammetric signal (5%) was observed after 4 months of storage. In order to study the repeatability, five modified electrodes based on the same fabrication process were used for the determination of 5.32×10^{-5} M RR-ETB and SS-ETB individually. The relative standard deviation (R.S.D.) for the I_p of all the five electrodes (average of five determinations) was calculated to be 2.1%. The above results ascertain that the CD-CuMOF-CNF-GCE has excellent stability and high reproducibility for determination of ETB isomers.

3.7. Application of the chiral electrochemical sensor in pharmaceutical and real sample analysis

The estimation of RR-ETB and SS-ETB in serum and urine samples from healthy volunteers was performed and results are shown in Table 1 respectively. The amount of RR-ETB and SS-ETB in all samples was determined using standard addition method. Also, the proposed method was used for formulation of pharmaceutical sample (Table 1). Recovery results were not affected significantly and consequently the proposed method is accurate for the determination of SS-ETB in pharmaceutical formulations and for both isomers separately (RR-ETB and SS-ETB) in biological fluids. The amounts of RR-ETB in pharmaceutical formulations agree well with the label contents. HPLC was used for comparison of proposed method and result was found to be satisfactory (Table 1).

Table 1. The values of stability constant and Gibbs free energy for enantiomer complex of ETB. Precision and accuracy of SS-ETB in spiked biological fluids (n = 4) and recovery in pharmaceutical samples (n = 5) at CD-CuMOF-CNF-GCE by the voltammetric method.

Stability constant and Gibbs free energy for enantiomer complex of ETB		
Enantiomer Complex	Stability constant (K) (M^{-1})	Gibbs free energy (ΔG) ($kJmol^{-1)}$
[CD-CuMOF (SS-ETB) $(H_2O)_2$]$^{2+}$	6.109 x 10^5	-33.01
[CD-CuMOF (RR-ETB) $(H_2O)_2$]$^{2+}$	1.088 x 10^5	-27.73

Precision and accuracy of SS–ETB in spiked biological fluids			
Real samples	Added Concentration (10^{-5} M)	Obtained Concentration (10^{-5} M)	Average Recovery (%) ± R.S.D (n = 4)
Serum	–	N.D	–
	2.58	2.53	98.06 ± 1.6
	2.62	2.58	98.47 ± 1.0
Urine	–	N.D	–
	3.59	3.54	98.60 ± 2.2
	5.17	5.16	99.80 ± 1.8

Pharmaceutical Samples	**Amount of SS-ETB obtained by**				
	Proposed method			**HPLC method**	
	Labeled / tablet (mg)	Found / tablet (mg)	Average recovery (%) ± R.S.D (n = 5)	Found / tablet (mg)	Average recovery (%) ± R.S.D (n = 5)
Myambutol	400	399.12	99.68 ± 1.70	399.16	99.79 ± 0.65
Albutol	200	198.98	99.49 ± 0.58	199.15	99.57 ± 0.38

4. Conclusion

The synthesized chiral β-cyclodextrin/copper metal organic framework studies established that on the surface of electrode, isomers of the same ethambutol molecule show different redox behaviour with excellent enantioselectivity employing square wave voltammetry. The formation of diastereomeric complex with isomers paved the way for recognition mechanism. This sensing device might be easily customized and extended towards the rapid screening system of pure API among contaminated mixtures with RR-ETB in blood, urine or pharmaceutical samples. CD-CuMOF displays the potential to be: i) New class of chiral selector, ii) Enzyme mimic for chiral drugs and iii) Excellent material for enantiomer discrimination for biomolecules not only by electrochemical methods but also using other analytical techniques.

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Highlights

- Enantioselective sensor for ethambutol isomers using CD, CuMOF and CNF composite on GCE using SWV
- CD-CuMOF as an artificial enzyme model for determination of ethambutol enantiomers
- The constructed chiral electrode has exhibited higher affinity for SS-ETB than RR-ETB
- Mechanism of chelate complexation and enzyme mimicking process of ETB with CD-CuMOF is explained
- Analysis of ethambutol enantiomers in racemic mixture, pharmaceutical and biological samples

Declaration of interests

X The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: