

## Zinc Oxide Nanoflowers Based Graphene Nanocomposite Platform for Catalytic Studies of Febuxostat

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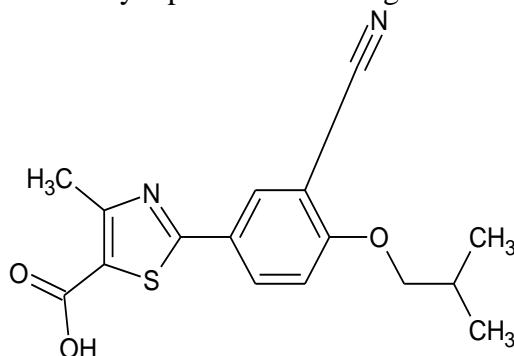
A novel graphene/zinc nanoflowers nano-composite modified glassy carbon electrode (GR/ZnOnFs/GCE) based electrochemical transducer system has been developed for the sensitive voltammetric analysis of a muscle relaxant drug febuxostat (FEB) in methyl alcohol at pH 6.5 Britton Robinson (BR) buffer. The developed GR/ZnOnFs/GCE) sensor was characterized by microscopic, spectroscopic and electrochemical techniques to get significant information about the morphology, composition and sensing performance of the developed electrode towards reduction of FEB. Various kinetic parameters affecting the monitored electrocatalytic response were evaluated. SWV studies shows linear response between increasing concentrations of FEB (10-400 ng mL<sup>-1</sup>) and cathodic current with correlation coefficient ( $r^2$ ) of 0.9954 with reproducibility of 3.26%. The sensing utility of proposed sensor was extended to *in vitro* determination of the drug in pharmaceutical formulation and in waste water with an acceptable recovery and reproducibility. The fabricated (GR/ZnOnFs/GCE) sensor holds great promise for simple and sensitive quantification of febuxostat using electroanalytical techniques.

**Keywords:** Zinc oxide nanoflowers, Graphene, Febuxostat, Voltammetry, Nanocomposite

### 1. INTRODUCTION

Nanofabrication and processing of various electrochemical sensors, exhibit increased sensitivity and selectivity towards various redox processes [1-4]. Concept of chemically modified electrodes (CMEs) has been flourishing since last few years to produce sensors of enhanced catalytic properties for detection of various desirable target compounds [5-7]. In recent years, subject of development of advance functional materials at nanoscale as chemical modifiers has taken a new dimension in terms of their wide ranging potential applications in electrochemistry [8-10].

In last few decades, graphene (GR), a carbon based  $sp^2$  hybridized 2D sheet of graphite, have emerged as a novel sensing material for fabrication of chemically modified working electrodes. GR has a wide and diverse impact on fabrication and preparation of sensors and in electrocatalysis for screening a wide variety of compounds [11-13]. Also, apart from carbon based CMEs, various metal oxides (MOs) have also attracted attention for their use as electrode materials. Among various MOs, Zinc oxide (ZnO) nanostructures are promising materials for various applications in electroanalytical sensing having high effective electrode surface area, high ion mobility, stable biocompatibility, high thermal stability and piezoelectricity [14]. Featuring outstanding catalyzing properties of GR and ZnO, their novel nanocomposite is quite interesting for studying electrode kinetics [15-22]. Along with providing larger active accessible electrode areas for the adsorption of target analytes, GR-ZnO nanohybrid accelerate the ion transfer between electrode surface and detection molecules leading to enhanced current response for voltammetric sensing [23-31]. Significant chemically modified electrodes have been prepared and widely reported for sensing of various target moities [32-38].



[2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid]

The present work reports a defined methodology for the synthesis and fabrication of graphene based crystalline nano flowers ZnO modified glassy carbon electrode (GR/ZnOnFs/GCE) and its successful application for electrochemical sensing of febuxostat (FEB), chemically 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid, a non purine inhibitor of xanthine oxidase in methyl alcohol at pH 6.5 (BR buffer) [35, 39-41]. Electrochemical performance of the developed GR/ZnOnFs/GCE electrode has been evaluated for the reduction studies of FEB using voltammetric techniques. The fabricated GR/ZnOnFs/GCE sensor was found to have acceptable recovery limits in pharmaceutical tablets and in waste water and hence justified for its analytical utility for sensing applications.

## 2. EXPERIMENTAL

### 2.1 Reagents and chemicals

Febuxostat reference standard (99.6% purity) was provided by Sun Pharmaceuticals Pvt. Ltd., Varodara, India and was used as received. Tablets containing FABUTAZ (40 mg by Sun Pharmaceuticals Pvt. Ltd., Sikkim) were obtained from local pharmacy. Graphene (97% purity) was

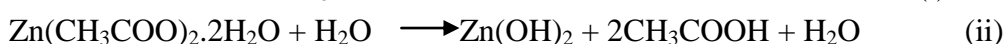
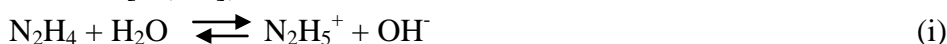
obtained from Graphene Laboratories USA. All chemicals and reagents used were of analytical reagent grade and utilized without further purification.

## 2.2 Apparatus

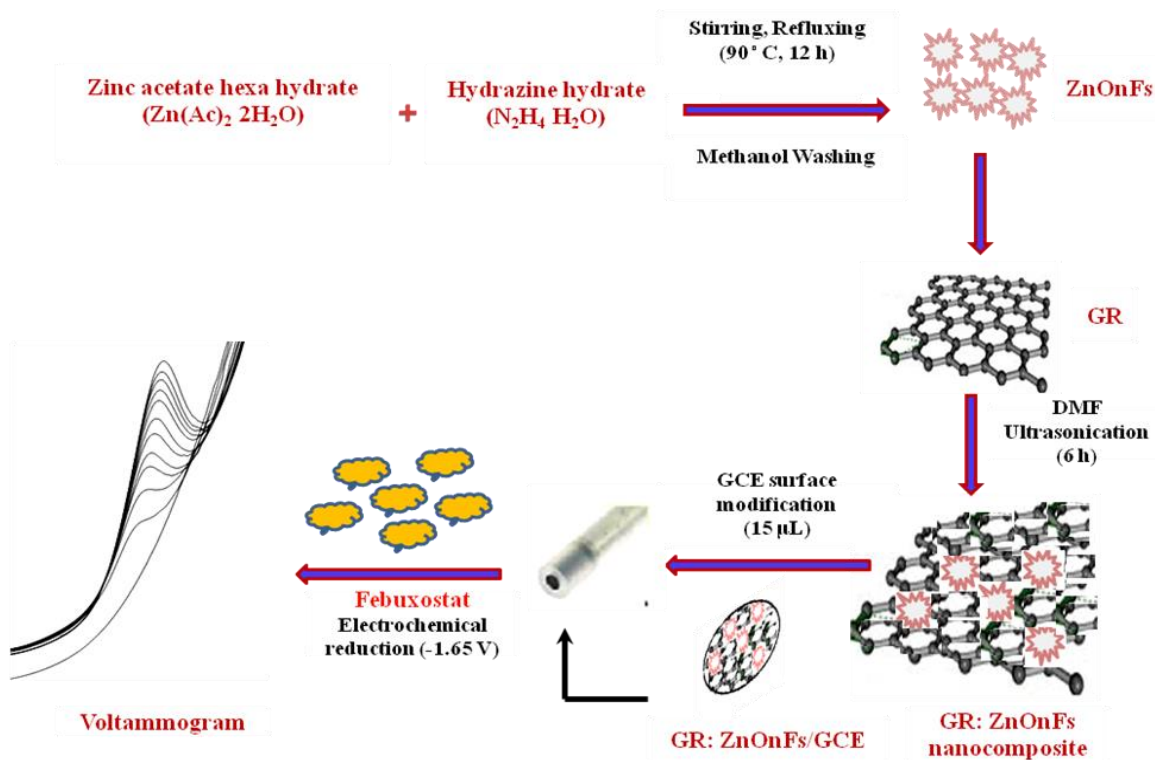
Electrochemical measurements were performed using a  $\mu$ -AUTOLAB TYPE III (Eco-Chemie B.V., Utrecht, The Netherlands) potentiostat-galvanostat with NOVA 1.10 software. Fabricated GR/ZnOnF/GCE was employed as working electrode, Ag/AgCl (3.0 mol/L KCl) was used as reference electrode and platinum wire as a counter electrode. The morphological characteristics of electrodes were studied by scanning electron microscope using ZEISS EVO 50 instrument. Synthesized zinc oxide nano flowers (ZnOnFs) were characterized by Fourier transform infrared spectroscopy (FTIR) using IR-SPECTRUM GX Perkins Elmer USA. X-ray diffraction pattern of fabricated ZnOnFs were recorded with an X Ray diffractometer (D/MAX2500PC) using Cu K $\alpha$  radiation of wavelength  $\lambda = 1.5406$  nm. All the pH-metric measurements were carried at Decible DB-1011 digital pH meter.

## 2.3 Synthesis of zinc oxide nanoflowers and fabrication of GR/ZnOnFs/GCE modified sensor

Zinc nanoflowers were synthesized by a simple chemical approach. Zinc acetate dehydrate ( $\text{Zn}(\text{Ac})_2 \cdot 2\text{H}_2\text{O}$ ) of about 6.82 g was mixed with 25 mL of hydrazine hydrate ( $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ ) and stirred for 30 min till a white coloured precipitate was obtained. It was refluxed for 12 h at 90° C resulting in a pure white coloured precipitate (ZnO) which was then washed with methanol followed by vacuum filtration and collected after drying. The reactions involved in the synthesis of zinc oxide nanoflowers are given below [19, 38],



A homogenous GR suspension and synthesized ZnOnFs were prepared in 1:1 ratio and dispersed in N, N- dimethylformamide (DMF) resulting in a solution of 1 mg mL<sup>-1</sup> after ultrasonication for 6 h. Prior to analysis, bare GCE was properly washed and rinsed with ultra pure water. The GCE surface was polished with alumina powder (0.05  $\mu\text{m}$ -0.1  $\mu\text{m}$ ) on microcloth pads and washed with ultrapure water several times till a clean surface finish was obtained. A known volume of the GR/ZnOnFs/DMF suspension (15  $\mu\text{L}$ ) was drop casted at the bare GC surface using a microsyringe and employed for the voltammetric measurements for detection of FEB (Scheme 1).

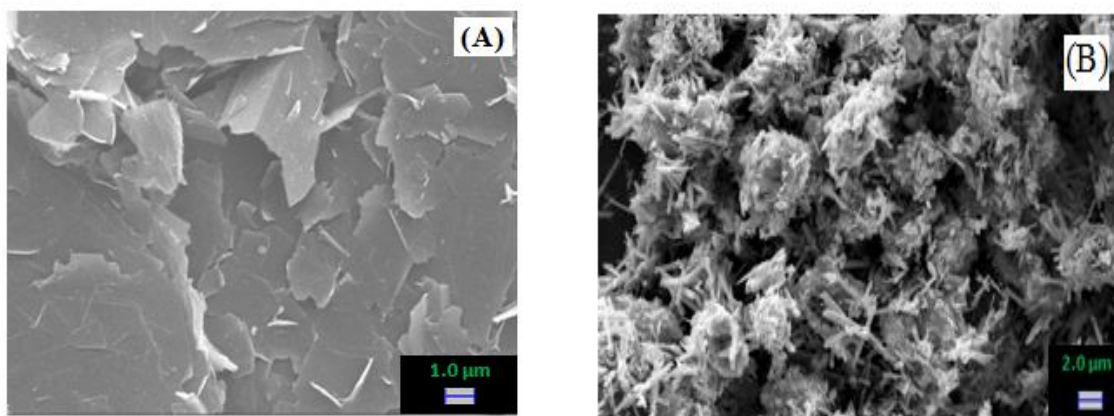


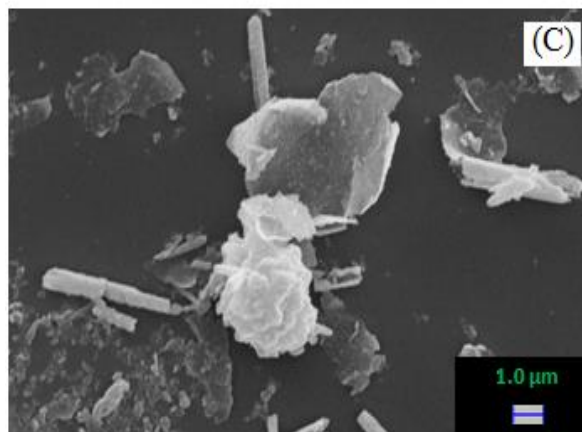
Scheme 1. Fabrication process of GR/ZnOnFs/GCE for FEB reduction

### 3. RESULTS AND DISCUSSION

#### 3.1 Scanning electron microscopy

Fig. 1A and 1B show the scanning electron micrographs of GR sheets and synthesized flower shaped zinc oxide nanostructures (ZnOnFs) respectively which clearly confirm the formation of GR/ZnOnFs nanocomposite in Fig. 1C retaining their original morphology. ZnOnF are clearly seen spread over GR sheets suggesting the GR/ZnOnFs nanoconjugate system.

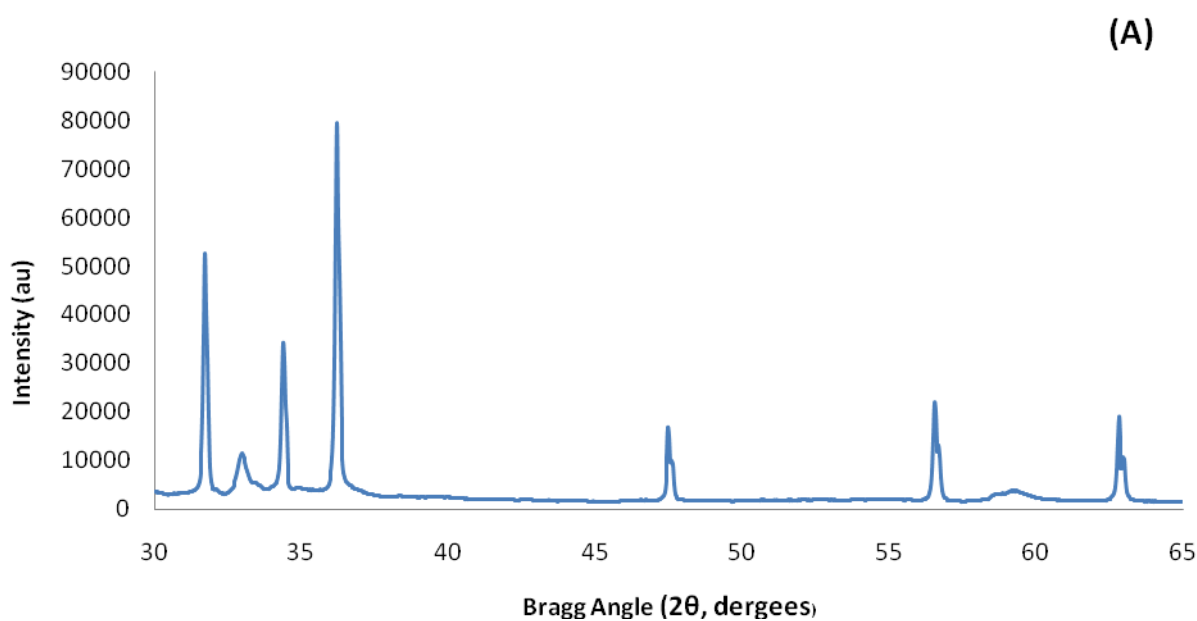


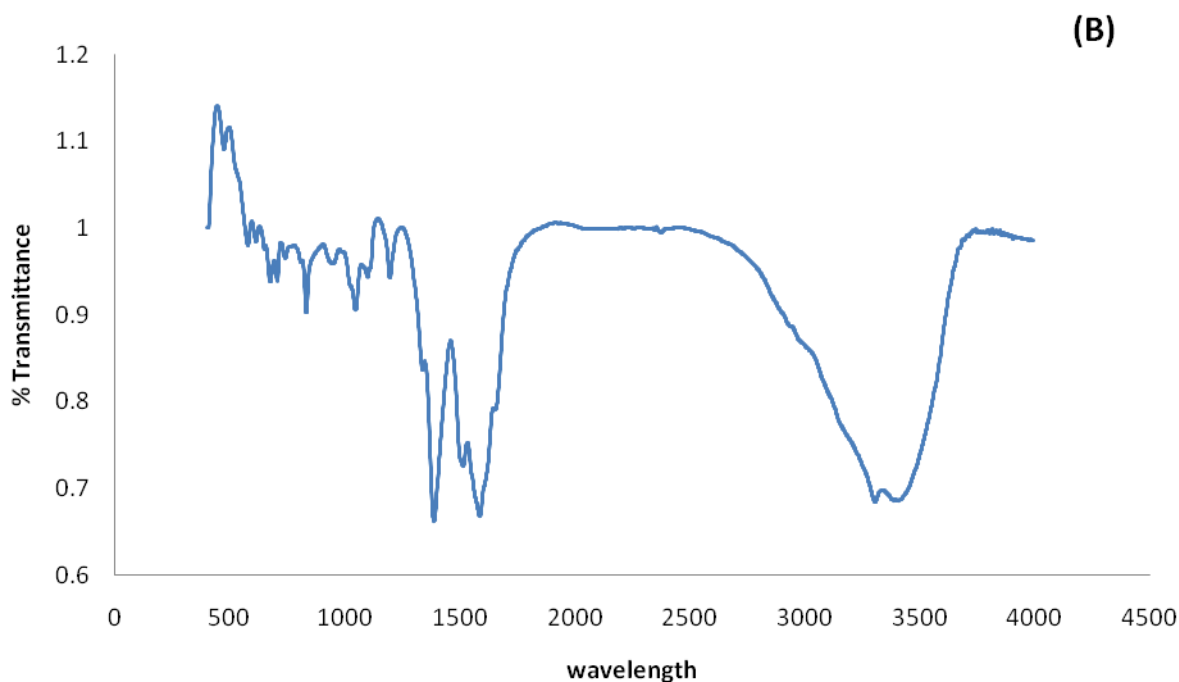


**Figure 1.** Scanning electron micrograph of (A) GR (B) ZnOnFs (C) GR/ZnOnFs

### 3.2 XRD and FTIR studies

Formation of crystalline zinc oxide nanoflowers is confirmed with sharp, intense and well defined X ray diffraction pattern in the range of  $30^\circ < 2\theta < 65^\circ$  at Cu  $K\alpha$  radiation of wavelength  $\lambda = 1.5406$  nm which is in well agreement with the previous reports [19-22] (Fig. 2A). Fourier transform infrared spectroscopy (FTIR) was performed by in the range  $400-4000$   $\text{cm}^{-1}$  for characterizing ZnOnF (Fig. 2B) [42]. FTIR spectra show a strong peak between  $400-550$   $\text{cm}^{-1}$  for Zn—O bond. The appearance of the bands near  $1394$   $\text{cm}^{-1}$  and  $1507$   $\text{cm}^{-1}$  correspond to C=O vibration of acetate in the metal-acetate bonding present in the ZnO nanoflowers.





**Figure 2.** (A) XRD pattern (B) FTIR spectra of zinc oxide nanoflowers

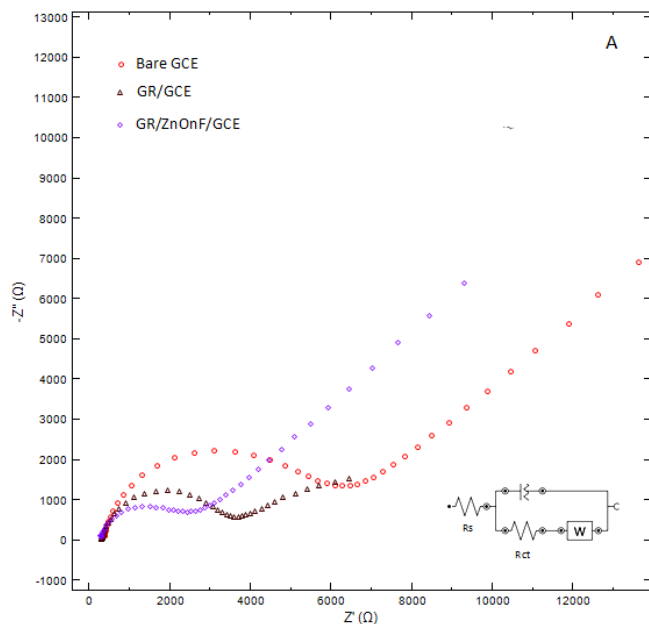
The broad band at  $3400\text{ cm}^{-1}$  is assigned for the O-H moieties in the sample. The band near  $900\text{ cm}^{-1}$  and  $1050\text{ cm}^{-1}$  are ascribed as stretching vibrations of C-O group which further suggests the surface attachment of acetate group to ZnO. The band near  $1650\text{ cm}^{-1}$  is assigned as the bending vibrations for surface adsorbed  $\text{H}_2$

### 3.3 Electrochemical measurements

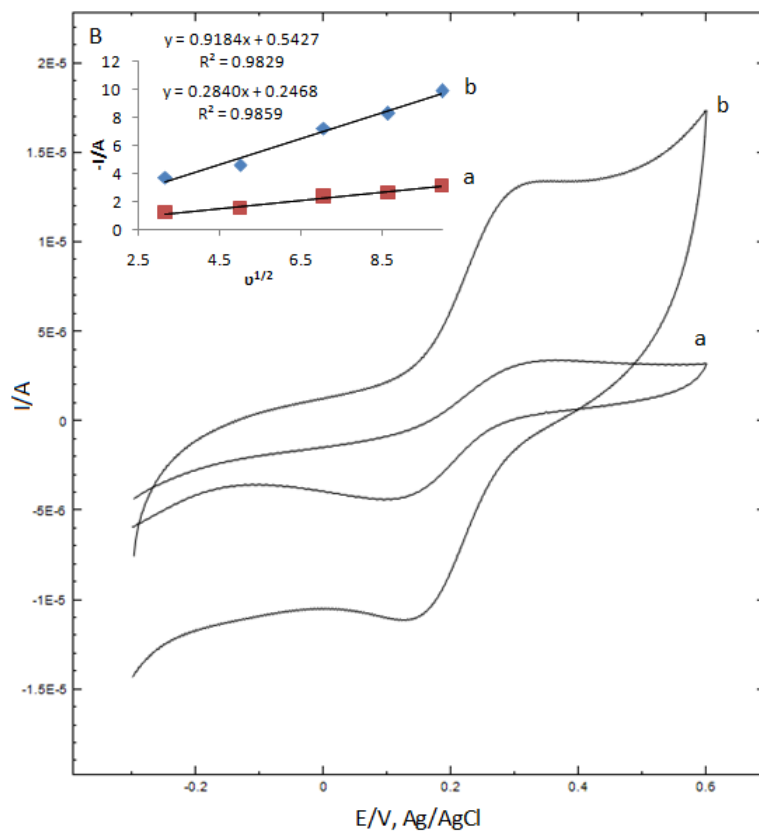
Electrochemical impedance spectroscopy (EIS) was performed to compare the charge transfer resistance ( $R_{ct}$ ) of the developed electrodes taking  $5.0\text{ mM K}_3\text{Fe(CN)}_6^{-3/4}$  as redox probe. Using appropriate equivalent circuit, the measured values of  $R_{ct}$  for different electrodes were obtained as  $1.37\text{ k}\Omega$  for GR/ZnOnFs/GCE,  $2.48\text{ k}\Omega$  for GR/GCE and  $4.24\text{ k}\Omega$  for bare GCE respectively. In the high frequency region, a decreased diameter of the semicircle was observed for GR/ZnOnFs/GCE electrode suggesting its higher electronic conductivity and ion transfer for electrocatalytic reduction of FEB compared to GR/GCE and bare GCE (Fig. 3A).

Effective surface area of the fabricated electrode was calculated by cyclic voltammetry using  $1\text{ mM K}_3\text{Fe(CN)}_6$  in  $0.1\text{ M KCl}$  as redox standard redox. The slope of the current plot ( $I$ ) and the square root of scan rate ( $v^{1/2}$ ) (Fig. 3 B) possess a linear relationship justified by the employing Randles Savcik equation 
$$I = (2.69 \times 10^5) ACD^{1/2} n^{3/2} v^{1/2}$$
 Where,  $A$  is the surface area of the electrodes in  $\text{cm}^2$ ,  $n$  is the number of electrons involved in the reduction process,  $D$  is the diffusion coefficient of the analyte in the solution and  $C$  is the concentration of the drug sample in the solution which are  $7.6 \times 10^{-6}\text{ cm}^2\text{ s}^{-1}$  and 1 respectively [43].

The effective surface area of GR/ZnOnFs/GCE was found as 2.28 cm<sup>2</sup> confirming higher catalytic activity than bare GCE (1.56 cm<sup>2</sup>) that can be attributed to surface modification.

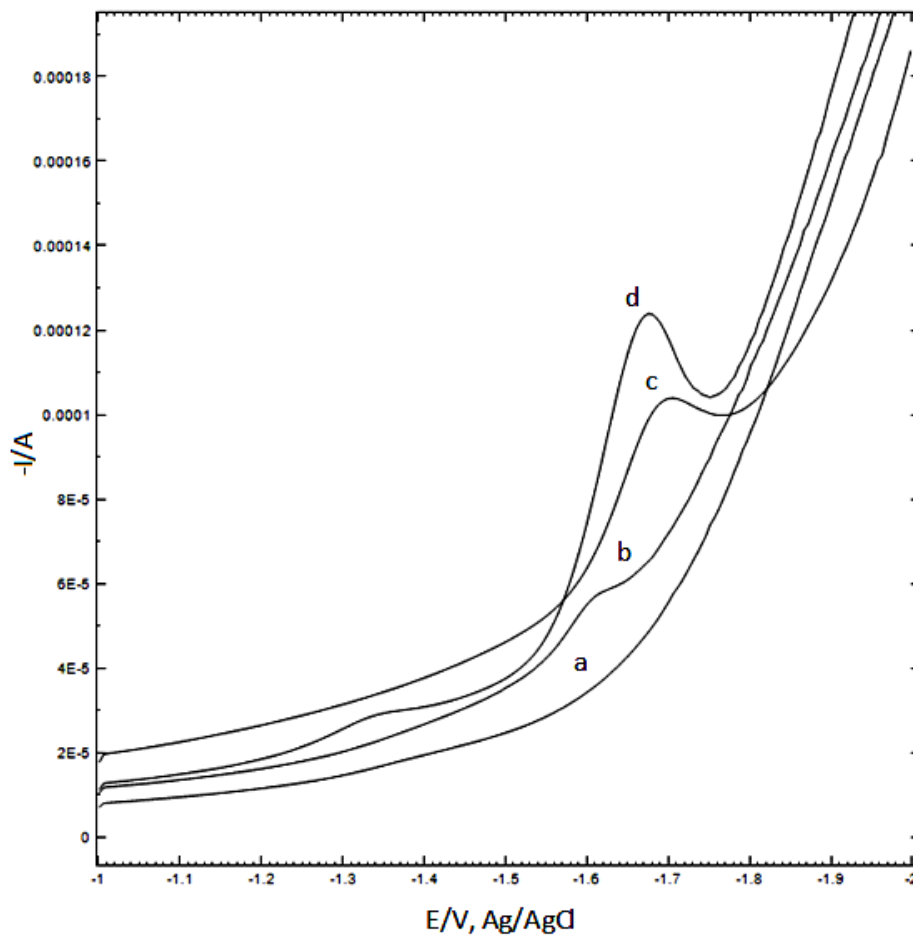


**Figure 3 A.** Nyquist plot obtained for different electrodes in 5.0 mM K<sub>3</sub>Fe (CN)<sub>6</sub><sup>-3/4</sup>



**Figure 3 B.** Cyclic voltammetric behaviour of 1mM K<sub>3</sub>Fe(CN)<sub>6</sub> at bare GCE (curve a), at GR/ZnOnFs/GCE (curve b), Inset: Calibration plot of current (I) vs. square root of scan rate ( $v^{1/2}$ )

Under optimized conditions [35], electrocatalytic reduction of FEB was studied by square wave voltammetry (SWV) at GR/ZnOnFs modified GC electrode. It was found that  $200.0 \text{ ng mL}^{-1}$  of FEB in methyl alcohol alcohol in Britton Robinson buffer at pH 6.5 exhibits a well defined cathodic peak (Fig. 4) Obtained voltammogram clearly show that the GR/ZnOnFs modified GC surface is much more sensitive towards reduction of FEB and confirms the improved electrocatalytic performance of GR/ZnOnFs/GCE than GR/ GCE and bare GCE sensor.



**Figure 4.** Square wave voltammogram obtained for reduction of FEB at (a) blank, (b) bare GCE, (c) GR/GCE and (d) GR/ZnOnFs/GCE

### 3.3 Proposed electrode reaction

Taking two as the number of electron involved in the electrode process of febuxostat [35], reduction mechanism for febuxostat at GR/ZnOnFs/GCE has been postulated as scheme 2.





obtained (Fig. 5) showed that peak current increased linearly with increasing concentration of FEB over a wide concentration range from 10-400 ng mL<sup>-1</sup> that signifies the enhanced sensing performance of GR/ZnOnFs/GCE sensor towards reduction of FEB. A linear calibration plot was drawn and expressed by the following equation (ii),

$$I/A = 0.0086 (\text{ng mL}^{-1}) + 1.2835, r^2 = 0.9954 \quad (\text{ii})$$

Limit of detection (LOD) and limit of quantification (LOQ) were calculated as 3S/m and 10S/m respectively where S represents the standard deviation of the intercept and m is slope of regression line. The LOD and LOQ for the proposed voltammetric study are found to be 1.84 ng mL<sup>-1</sup> and 6.16 ng mL<sup>-1</sup> respectively.

### 3.5 Reproducibility and stability of GR/ZnOnFs/GCE sensor

The reproducibility of the GR/ZnOnFs/GCE sensor was studied using SWV taking 200.0 ng mL<sup>-1</sup> of FEB at three different electrodes fabricated at different time intervals. Table 1 exhibits the reproducibility data of the sensor with RSD of 3.26%. Further, the sensor was checked for its stability studies. The cathodic current response of 200.0 ng mL<sup>-1</sup> of FEB was evaluated for 25 days. In between the fabricated sensor was stored at 4°C. After 25 days the sensor exhibits 78% of its initial current response.

**Table 1.** Reproducibility data for 200 ng mL<sup>-1</sup> FEB at GR/ZnOnFs/GCE sensor

Sensor <sup>a</sup>	Current (I/A)
Sensor 1	2.87 <sup>a</sup>
Sensor 2	2.74 <sup>a</sup>
Sensor 3	2.92 <sup>a</sup>
Average	2.84 <sup>b</sup>
RSD %	3.26

<sup>a</sup> Mean of eight replicate readings, <sup>b</sup> Mean of three sensors

### 3.6 Accuracy and Precision

Accuracy and precision of the proposed method was calculated by incorporating the three different concentrations (150.0, 250.0, 350.0 ng mL<sup>-1</sup>) of FEB standard. The percentage relative error between the found mean concentration and the added concentration established the accuracy of the proposed sensor. The precision was justified in terms of the relative standard deviation (% R.S.D) and coefficient of variation. Results obtained (Table 2) were in good agreement for the accuracy and precision of the proposed method.

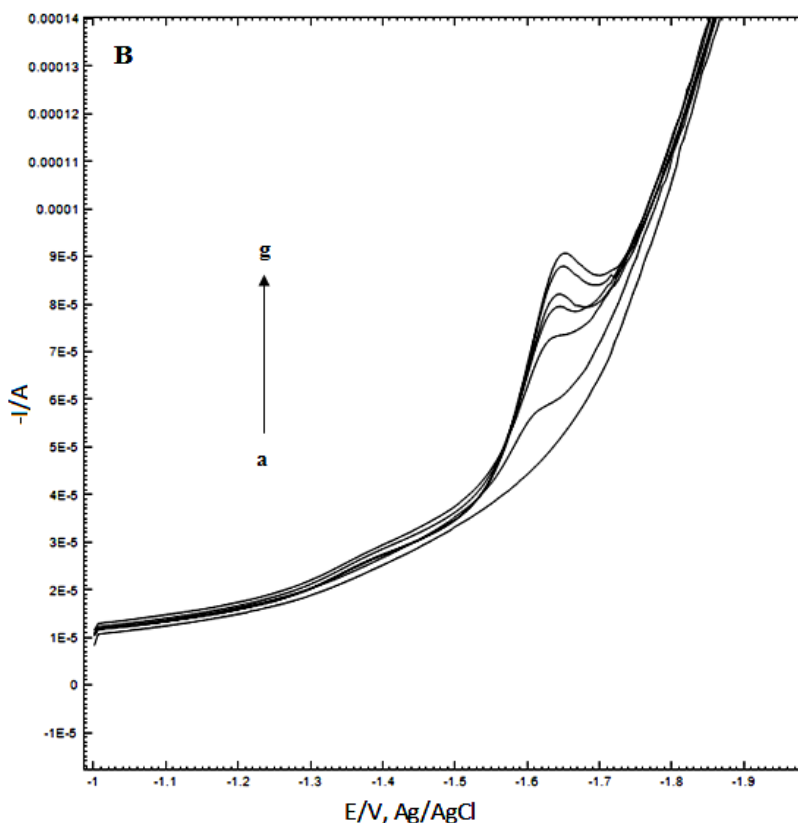
**Table 2.** Accuracy and precision for determination of febuxostat by SWV (n=5).

Added (ng mL <sup>-1</sup> )	Found (ng mL <sup>-1</sup> )	Precision <sup>a</sup> (ng mL <sup>-1</sup> )	Coefficient of variation (%)	Accuracy <sup>b</sup> (%)
150.0	145.19	145.19 ± 1.43	0.98	-4.80
250.0	254.68	254.68 ± 1.16	0.45	4.68
350.0	346.88	346.88 ± 4.05	1.16	-3.11

<sup>a</sup>Mean ± Standard Deviation, <sup>b</sup> Accuracy = [ found – added/added] × 100, Coefficient of variation = S.D./Mean × 100

3.7 Analytical applications of the proposed method

The performance of the fabricated sensor was investigated to establish for analytical applications. At fabricated GR/ZnOnFs/GCE sensor, FEB was detected in commercial pharmaceutical tablets *FABUTAZ* labeled 40 mg manufactured by Sun Pharma, India.



**Figure 6.** Square wave voltammogram of FEB in waste water at GR/ZnOnFs/GCE at different concentrations, (a) blank, (b) 100.0 ng mL<sup>-1</sup>, (c) 150.0 ng mL<sup>-1</sup>(d) 200.0 ng mL<sup>-1</sup>, (e) 250.0 ng mL<sup>-1</sup>, (f) 300.0 ng mL<sup>-1</sup>, (g) 350.0 ng mL<sup>-1</sup>.

Three prepared concentrations of FEB (150.0, 250.0, 350.0 ng mL<sup>-1</sup>) was added to calculated the percentage recovery using square wave voltammetry. Table 3 shows the percentage recovery based on mean value of three replicate measurements ranging from 96.55% to 102.13% and with standard

deviation of 3.34% to 4.92%. Also FEB was detected in waste water to justify the environmental utility of the fabricated GR/ZnOnFs/GC sensor. Samples of waste water were collected from local community and filtered through whatmann filter paper. Again, a series of three concentrations of FEB (150.0, 250.0, 350.0 ng mL<sup>-1</sup>) was spiked into waste water samples and analyzed according to the established methodology at GR/ZnOnFs/GCE sensor (Fig. 5B). Percentage recovery for detection of FEB in waste water was calculated between the acceptable limits of 97.26% to 104.35% with standard deviation of 2.86% to 4.81%. The results (Table 3) clearly suggest the established methodology of FEB detection in pharmaceutical formulations and waste water samples for analytical and environmental applications.

**Table 3.** Recovery studies of FEB in pharmaceutical formulation and waste water

In Commercial Tablets				
Added (ng mL <sup>-1</sup> )	Found <sup>a</sup> (ng mL <sup>-1</sup> )	RSD (%)		Recovery (%)
150.0	153.19	3.21		102.13
250.0	241.39	1.49		96.55
350.0	343.62	0.97		98.02
In Waste Water Samples				
Added (ng mL <sup>-1</sup> )	Found <sup>a</sup> (ng mL <sup>-1</sup> )	RSD (%)		Recovery (%)
150.0	156.53	1.82		104.35
250.0	243.16	1.30		97.26
350.0	343.62	0.97		97.64

<sup>a</sup> Mean of three replicates

### 3.8 Comparison of the proposed method with other reported methods

The proposed voltammetric method for FEB detection at GR/ZnOnFs/GCE sensor has been compared with the previous reported methods interms od detection limit (Table 4A) [35, 41, 44-49]. Moreover, a comparison for analysis of various analytes at GR/ZnO sensor has been also tabulated in table 4B [23-31]. Obtained results reveal that the developed method of FEB quantification is very sensitive at GR/ZnOnFs/GCE sensor.

**Table 4 A.** Comparison of detection limit of FEB reduction with other reported methods

Reference method	Limit of detection	Reference
RP-HPLC I	0.5 $\mu\text{g mL}^{-1}$	[44]
RP-HPLC II	0.018 $\mu\text{g mL}^{-1}$	[41]
RP-HPLC III	1.16 $\mu\text{g mL}^{-1}$	[45]
RP-HPLC IV	9.98 $\mu\text{g mL}^{-1}$	[46]
RP-HPLC V	0.02 $\mu\text{g mL}^{-1}$	[47]
LC-MS	0.0025 $\mu\text{g mL}^{-1}$	[48]
UV Spectrophotometry	0.17 $\mu\text{g mL}^{-1}$	[49]
Voltammetry MWCNTs/AlTi/GCE	25.73 $\text{ng mL}^{-1}$	[35]
Voltammetry GR/ZnOnFs/GCE	1.84 $\text{ng mL}^{-1}$	Present work

**Abbreviations:** RP-HPLC: reverse phase high performance liquid chromatography, LC-MS: liquid chromatography mass spectroscopy, MWCNTs: multi walled carbon nanotubes, AlTi: Aluminium Titanate, ZnOnF: zinc oxide nanoflowers, GCE: glassy carbon electrode.

**Table 4 B.** Comparison of determination of other analytes at GR/ZnO sensor

Sensor	Analyte	Detection Limit	Reference
ZnO-rGO	Ascorbic acid	$0.01 \times 10^{-6}$	[23]
G-ZnO	$\text{H}_2\text{O}_2$	$7.43 \times 10^{-6}$	[24]
rGO-ZnO	Glucose Oxidase	$200 \times 10^{-6}$	[25]
GN/ZnO/SPCE	Glucose	$70 \times 10^{-6}$	[26]
GR/ZnO	$\text{H}_2$	-	[27]
RGO/ZnO	Glucose Oxidase	$20 \times 10^{-6}$	[28]
GR/ZnONPs	Cholesterol Oxidase	$5.0 \times 10^{-6}$	[29]
GR/CNT/ZnO	Glucose Oxidase	$200 \times 10^{-6}$	[30]
GR/ZnONR	$[\text{Fe}(\text{CN})_6]^{3+}$	$1.0 \times 10^{-6}$	[31]
GR/ZnOnFs/GCE	Febuxostat	$5.81 \times 10^{-9}$	Present work

**Abbreviations:** RGO, reduced graphene oxide; G, Graphene; GR, graphene; ZnO, zinc oxide; GN, graphite nano sheets; SPCE, screen printed carbon electrode; ZnONPs, zinc oxide nanoparticles; CNT, carbon nanotubes; ZnOnFs, zinc oxide nanoflowers

#### 4. CONCLUSION

Synthesis of flower shaped catalyzing nanostructure based on ZnO and its GR conjugate (GR/ZnOnFs/GCE) modified GCE sensor has been successfully developed with for electrochemical reduction studies of FEB using voltammetric techniques. Surface modification of bare GCE with GR/ZnOnFs nanocomposite significantly enhances the electrochemical performance of the fabricated sensor as compared to unmodified bare GC electrode surface. A sensitive electrochemical method based on ZnOnFs-GR nanocomposite sensor was developed for routine determination of FEB in commercial tablets and in waste water system with high sensitivity and excellent selectivity.

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