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Development and Validation of Potentiometric ZnO Nanorods Modified Ion Selective Electrode for Determination of Gemifloxacin in Pharmaceutical Formulation

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Abstract

Potentiometric method for determination of Gemifloxacin (GEMI) by ion selective electrode based on ZnO nanorods incorporation with HPβ-CD as sensing ionophore and (KTFPB) potassium tetrakis- (3,5(Triflouromethyl) Phenyl Borate) ion as anionic site (additive) in Polyvinyl Chloride (PVC) membrane, without inner reference solution was developed. The sensor shows `nearly Nernstian response over a concentration range (0.5-10000 µM) with a slope of 33.65 mv decade-1 of concentration with a Limit of Detection (LOD) 0.1500 µM. The electrode exhibits a fast dynamic response of 2 s for a period of 6 months without significant change in its characteristics with excellent stability and sensitivity toward inorganic species. The method is accurate and precise as indicated by the mean recoveries 106.43% with RSD less than 2%. The proposed method was successfully applied for the determination of GEMI in pharmaceutical formulations.

Keywords

Potentiometric, Ion selective electrode, Zno nanorode, GEMI, PVC membrane

Introduction

Gemifloxacin Mesylate (GEMI), chemically known as [(R, S)-7-[(4Z)-3 (aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1, 8-naphthyridin-3-carboxylic acid mesylate] Figure 1. Its fourth generation fluoroquinolone antibacterial agent having affinity towards bacterial topoisomerase IV, It has broad spectrum of activity against gram-positive and gram-negative bacteria [1]. GEMI has shown potent activity against other major pathogens involved in respiratory tract infections, including Haemophilus influenza and the atypical organisms, *Legionella pneumophila, Chlamydia* spp, and *Mycoplasma* spp [2]. Furthermore, the compound has shown potent activity against many organisms that cause urinary tract infections. The adverse reaction profile is similar to that of older members of this class [3]. The great bactericidal activity of GEMI is due to the presence of 4-oxo-3-carboxylic acid [4].

A number of analytical methods have been reported for the determination of GEMI in pharmaceutical formulation and biological samples. These include High Performance Liquid Chromatography (HPLC) [5], HPLC coupled with Mass Spectrometry (HPLC-MS) [6], Capillary electrophoresis [7], Gas Chromatography-Mass Spectrometry (GC-MS) [8], Spectrophotometery [9],

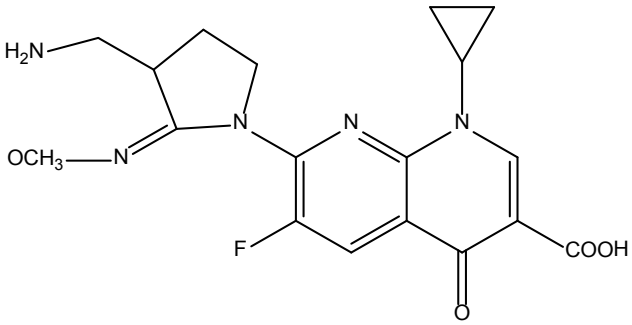

Figure 1: Chemical structure of Gemifloxacin.

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Spectrofluorimetry [10,11], Voltammetry [12] and Chemiluminescence [13]. Most of these methods are complicated involve derivatization procedures, requires intensive instruments also it's time and labor consuming.

Potentiometric sensors are easy to miniaturize and provides a large dynamic range. In conventional ion selective electrodes, Polyvinyl Chloride (PVC) is the most commonly used matrix as the selective membrane [14]. The ion-selective membrane exhibits the selectivity with which the sensing material responds to the analyte and an electrochemical equilibrium is reached. The resulting potential difference, formed between the phases, will then be governed by the activity of this specific ion in the two solution phases [15].

Potentiometric methods, using ion selective electrodes, have found wide application [16,17] being simple analysis procedures, economical coasts, fast results , applicable over a wide range of concentrations, applicability to various drug forms, with applicability to turbid and colored solutions, preciseness and offering enough selectivity towards the drug in the presence of various pharmaceutical excipients.

Al-Mohaimeed, et al. [16] developed potentiometric sensors using different such as ion-pairing agents Phosphotungstic Acid (PTA), Phosphomolybdic Acid (PMA) and Ammonium Reineckate Salt (ARS). The sensors exhibit good selectivity for GEMI with respect to some inorganic cations, amino acids and some pharmacologically related compounds [16]. Abo-talib demonstrated PVC membrane sensors for the determination of GEMI. The sensors are based on the use of the ion association complexes of GEMI cation with ammonium reineckate counter anions as ion exchange sites in the PVC matrix. The membranes incorporate ion association complexes of GEMI with dibutylsebathete, dioctylphthalate, nitrophenyl octyl ether. The proposed sensors were successfully applied for determination of GEMI in bulk powder, pharmaceutical formulation, and biological fluids [17].

Research on ZnO nanostructures have been fueled by the observation that the material properties depend not only on the composition but also on the size and shape [18]. Recently, ZnO nanowires, nanorods and nanotubes have gained much attraction due to their high surface-to-volume ratio which makes them extremely sensitive to minute surface changes. In addition, one-dimensional ZnO nanostructures are promising for sensing due to their ease to grow vertically on almost any substrate [18-20].

The aim of this work is to develop and validate a simple, sensitive, rapid and miniaturized potentiometric ZnO nanorods based ion selective electrode without inner reference solution for the determination of GEMI in pharmaceutical formulations. Ion selective electrode consisted of PVC, dibutyl phthalate, 2-Hydroxypropyl)-β-cyclodextrin (HPβ-CD) and Potassium Tetrakis (3,5(TriFlouromethyl)Phenyl) Borate (KTFPB) as matrix, plasticizer, sensing ionophore and anionic additive, respectively were used to develop the sensor.

Materials and Methods

Chemicals and reagent

Gemifloxacin was obtained from (98%, Bayer AG, Leverkusen Germany), HPβCD (ionophore), Potassium Tetrakis (3,5(TriFlouroMethyl)Phenyl) Borate (KTFPB) (additive), PVC (high molecular weight), dibutyl phthalate (a plasticizer), Zinc Acetate (ZnAc), Hexamethylenetetramine (HMTA) ware purchased from sigma Aldrich (St.Louis, USA), silver wire (0.3 mm diameter), Na_2HPO_4, H_3PO_4, KOH, acetone, isopropanol, Tetrahydrofuran (THF), methanol, (all solvent with HPLC grade), Factive tablets (320 mg GEMI per tablet) [LG life science Ltd, Kore lisansiyla Abdilbrahim ilacsan.VeTic.A.S. Maslak/Istanbul 3.5.2016, 210/86], Deionized water.

Instrument and apparatus

pH/mv meter (PHS-3E) (China), Ag/AgCl reference electrode (Ω metrohm.Autolab, inner and outer filling by KCl 3 M. (Netherlands), sensitive balance, magnetic hot plate, thermometer, oven, SEM (Zeiss Evo LS 10.Germany).

Seed and growth ZnO nanorods

ZnO nanorods were grown by low temperature aqueous chemical method [19]. A silver wire (0.3 mm) was cut in the length of 5 cm and cleaned by acetone and isopropanol for 2 min in each solution followed by rinsing with deionized water and left to dry at room temperature. The silver wire was immersed three times in a seed solution prepared by mixing alcoholic solutions of KOH added drop wise to heated, stirred 0.03 M of zinc acetate the resulting solution was kept under stirring for 2 hours at 60 °C prior dipping , the wires was left to dry at room temperature. The ZnO was grown by suspending the pre-coated Ag wire in aqueous solutions contains 0.025 M ZnAc with equimolar concentration of HMTA. The beaker was placed in preheated oven at 70 °C to 5 hours. The wires were cooled down, washed by deionized water and left to dry over night. The ZnO nanorods were characterized by SEM (Zeiss Evo LS 10, Germany) Figure 2.

Coating ZnO nanorods with Ion selective membrane

ZnO nanorods were coated by ion selective membrane by mixing 33% PVC, 66% DBP plasticizer, 1.2% HPβ-CD (ionophore), 0.4% KTFPB (ionic additive) in

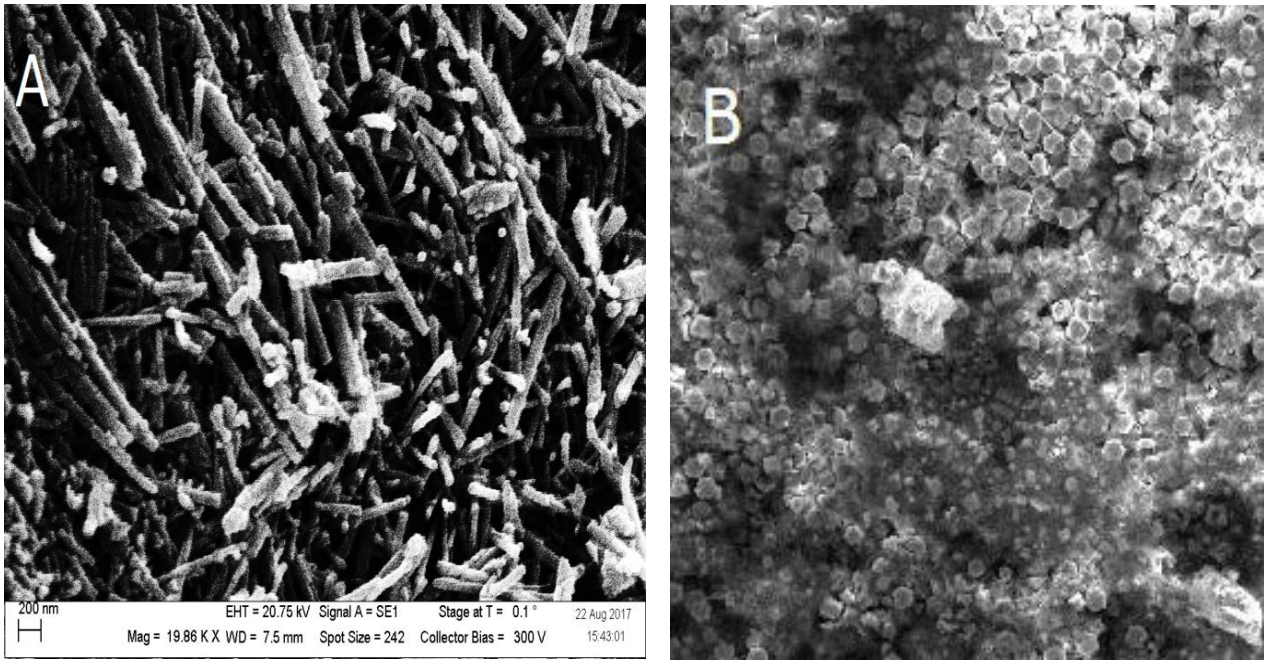

Figure 2: A,B) SEM at different magnifications and view of the ZnO nanorodes grown on Ag wire hydrothermal aqueous chemical method.

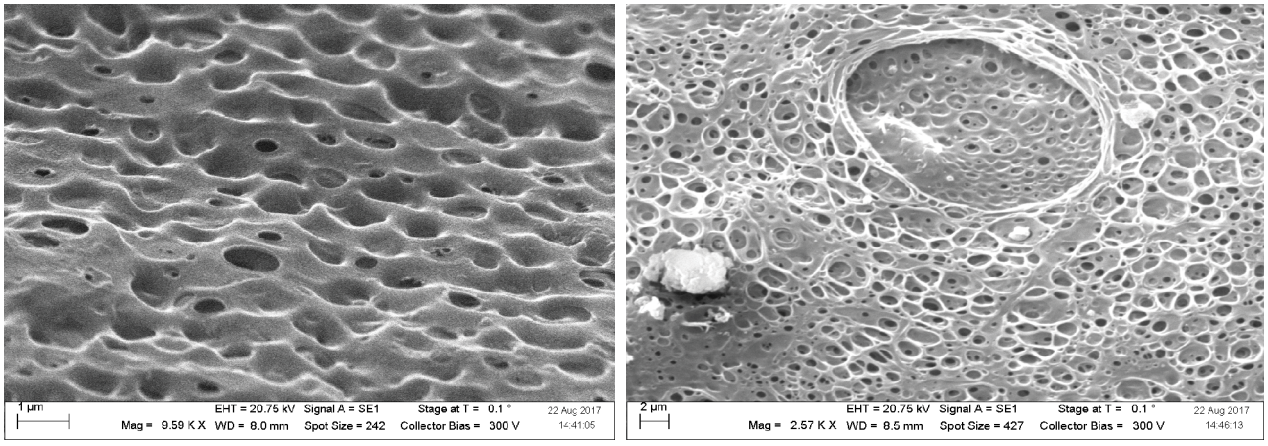

Figure 3: A,B) Presents ion selective membrane with KTFPB additive with different magnification.

5 GEMI-ZnO-seml THF. The ZnO coated wires was dipped twice into a prepared solution, after each dip the electrode was left to dry at room temperature, then the electrode was conditioned into 1×10^{-3} M of GEMI standard solution for 24 hour prior to use. The membrane was characterized by SEM (Zeiss Evo LS 10, Germany) Figure 3.

Standard drug solutions

Stock standard solutions 0.01 M GEMI (Mw = 389.381 g/mol) was prepared by dissolving accurate weight in 5 mL of 0.1 M NaOH and the volume was completed by deionized water, this solution was kept in the dark at 4 °C. Working solutions ranging 0.5-10000 µM were prepared by serial dilution of the stock solution by deionized water. The testing series was prepared by adding adequate amount of (0.2 M) phosphate buffer (H_3PO_4/Na_2HPO_4) [Ph = 3; 0.2 M] and desired volume of drug stock solution and the volume completed to mark by deionized water.

Preparation of GEMI sample solution

5 tablets of Factive (contain 320 mg GEMI per tablet) were weighed and the average weight was determined then it grounded into fine powder using mortar. Solution with 0.001 M was prepared by taken accurate weight of the powder dissolved by 5 mL of 0.1 M NaOH and 5 mL of phosphate buffer (H_3PO_4/Na_2HPO_4) [pH 3, 0.2 M] were added, the volume was completed to 250 mL by deionized water. The resulting solution was filtrated through filter paper.

Electrochemical measurements

In a complete potentiometric cell, the GEMI-ZnO-sem-

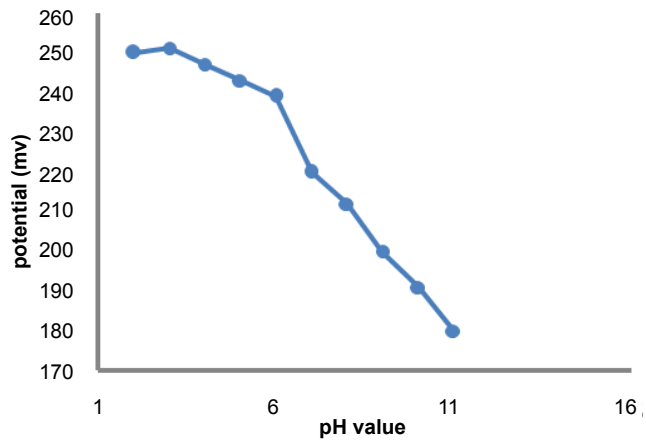

Figure 4: Optimization of pH for Gemi-TFPB-HPβ-CD, Gemi 1 × 10^{-4} M, at room temperature, time 2 sec.

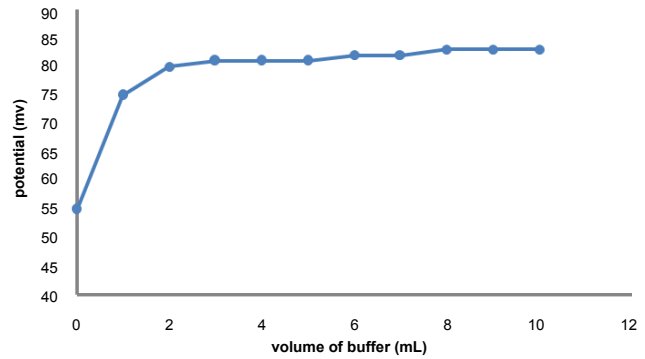

Figure 5: Optimization of volume buffer for Gemi-TFPB-HPβ-CD, Gemi 1 × 10^{-4} M, at room temperature, time, 2 sec, pH 3.

lective electrode was used in conjunction with Ag/AgCl reference electrode (inner and outer filling by KCl 3 M). The electrochemical potential between the GEMI-ZnO-selective electrode as cathode and Ag/AgCl reference electrode (Ω metrohm.Autolab, inner and outer filling by KCl 3 M) as anode was measured with pH/mv meter (PHS-3E).

GEMI.TFPB - PVC || Test solution || Ag/AgCl (3 M.KCl)

The measured potential was plotted against the logarithm of drug concentration. The electrode was washed with deionized water blotted with tissue paper between measurements.

Results and Discussions

Optimization conditions

Effect of pH: The effect of pH on the potential response of the GEMI-ZnO-ISE was investigated using 1 × 10^{-4} M solutions in pH range of 2.0-11.0 using Na_2HPO_4/H_3PO_4 (0.2 M) as a buffer solution. The potential readings corresponding to different pH values were recorded and plotted using the proposed electrode. Increasing in

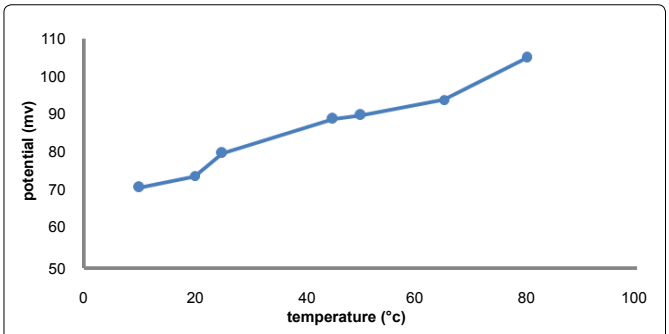

Figure 6: Optimization of temperature for Gemi-TFPB-HPβ-CD, emi 1 × 10^{-4} M, time 2 sec and 5 mL pH 3.

electrode potential was observed in pH range from 2 to 3 and decreased from pH 4 to 11, Figure 4. These result suggested that the inclusion complex of GEMI and HPβ-CD was suitable in acidic media because GEMI containing primary amine group that capable to bind with protons presents in acidic media resulting positively charged GEMI ion, which therefore can attracted by anionic tetraphenyl borate group present in the additive (KTFPB) and hence facilities the inclusion between GEMI and HPβ-CD [16,17,21].

Effect of volume of buffer: The effect of volume of buffer on the potential response of the GEMI-ZnO-ISE was studied using 1 × 10^{-4} M solutions in the range of (0-10) mL using Na_2HPO_4/H_3PO_4 [pH 3; 0.2 M]. It was found that the potential increased when buffer adding to GEMI solution without buffer and the potential remains constant with adding extra volume of buffer as shown in Figure 5.

Effect of temperature: The effect of temperature on the potential response of the GEMI-ZnO-ISE was studied using 1 × 10^{-4} M solutions at the range of temperature (10-80) °C using thermometer presented in Figure 6. It reveals that the potential increased with increasing temperature of drug solution this could be attributed to potentiometric measurements is equilibrium controlled [22], thus increasing solution temperature is resulting faster equilibrium between the electrode surface and GEMI solution.

Response time: The response time of potential of the GEMI-ZnO-ISE was studied using 1 × 10^{-4} M solutions in a period from 0 to 15 second. The potential readings corresponding to time were recorded and plotted using the proposed electrode in Figure 7. The sensor display very fast and response within 2 second.

Electrode composition

The electrode shows linear Nernestian response over a wide range of concentration 0.5-10000 µM, stable, sensitive and very fast response. This attributed to electrode compositions. The ZnO nanorods increased the surface

area for distribution of the membrane compared if it directly attached to silver wire, thus increased the sensitivity of the electrode and decreases the response time [18]. HPβ-CD is used as sensing ionophore, the most important property of CDs is their ability to form supramolecular inclusion complexes with many appropriately sized organic ions and molecules in aqueous, non-aqueous and mixed media [11]. The driving forces for the complexation are non-covalent, including Van der Waals forces and directed hydrogen bonding. Water molecules in CD cavity are displaced by more hydrophobic guest molecules present in the solution to attain a non-polar/non-polar association and decrease of CD ring strain resulting in a more stable lower energy state [23]. On constructing an ISE, the amount of the sensing ionophore in the electrode matrix should be sufficient to obtain reasonable complexation at the electrode surface that is responsible for the electrode potential [24,25].

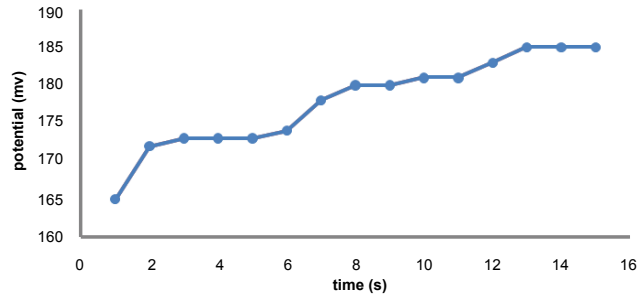

Figure 7: Optimization of response time for Gemi-TFPB-HPβ-CD, Gemi 1 × 10^{-4} M, time 2 sec and 5 mL pH 3.

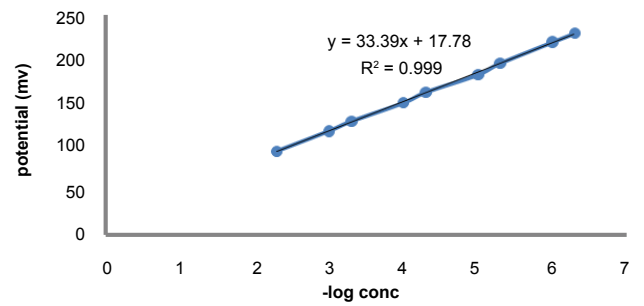

Figure 8: Calibration curve of Gemi-TFPB-HPβCD, Gemi 1 × 10^{-4} M, at room temperature, time 2 sec, 5 mL pH 3.

Table 1: Parameter for GEMI potentiometric method.

Parameter	Value
Intercept ± SD	16.76 ± 1.53
Slop	33.65
Correlation coefficient (R^2) linear	0.99929
Linear range (μM)	0.005-10000
LOD (μM)	0.1500
LOQ (μM)	0.4546
Response time	2 second
Life time	> 6 months
*PDL	0.001 Mm

*PDL = Practical Detection Limit.

The function of KTFPB as lipophilic ionic additives is to promote the interfacial ion exchange kinetics and decrease the electrode resistance through enhancing the ionic mobility in the electrode matrix. The response of ISEs containing ionic sites can be distinguished whether the incorporated ionophore acts as an electrically charged or uncharged carrier [26,27].

Statistical data

The analytical methods were validated with respect to linearity, Limit of Detection (LOD), Limit of Quantification (LOQ) and precision according to ICH [28,29].

Calibration curve and statistical data for GEMI: The measuring range of a potentiometric sensor was the linear part of the calibration graph as shown in Figure 8. The critical response coated wire sensor electrodes were determined and the results were summarized in Table 1. LOD and LOQ were determined using the formula: LOD or LOQ = K.SD a/b, where K = 3.3 for LOD and 10 for LOQ, SDa is the standard deviation of the intercept, and b is the slope. the values of LOD and LOQ were found to be 0.15 and 0.4546 μM respectively. The sensor show nearly Nernestian response over the concentration range 0.5-10000 μM of the GEMI standard solution. Calibration graph slope for sensor electrode were 33.65 mV de-

Table 3: Robustness of potentiometric method for GEMI determination.

Parameter	Value	Recovery % ± RSD*
Standard conditions		99.1 ± 0.44
pH	2.5	98.5 ± 0.39
	3.5	99.1 ± 0.45
Temperature (°C)	30	98.3 ± 0.29
	40	96.2 ± 0.63
Volume of buffer (ml)	2	99.3 ± 0.93
	8	98.7 ± 0.66
Reaction time (sec)	2	96.3 ± 0.74
	10	98.6 ± 0.48

(*values are mean of 3 determinations); RSD = (SD /mean*100).

Table 2: Precision of the potentiometric method for GEMI determination.

Concentration	Taken (-log C)	Found (-log C)	Recovery % ± RSD*
1 × 10^{-3} M	3	2.988	99.6 ± 1.12
5 × 10^{-5} M	4.3	4.356	101.3 ± 1.26
1 × 10^{-6} M	6	6.023	100.38 ± 1.74

*values are mean of three determinations; RSD = (SD /mean*100).

Table 4: Recovery of the potentiometric method of GEMI.

Sample content M	Standard added M	p [Concentration]	Found log [Concentration]	Recovery (% ± RSD)*
1×10^{-4}	1×10^{-4}	3.70	4.14	111.8 ± 0.64
1×10^{-4}	2×10^{-4}	3.52	3.64	103.41 ± 1.81
1×10^{-4}	3×10^{-4}	3.40	3.34	98.23 ± 0.77
1×10^{-4}	4×10^{-4}	3.30	3.16	95.76 ± 0.94
1×10^{-4}	5×10^{-4}	3.22	3.07	95.28 ± 0.83

cade^{-1}. The electrodes exhibited a fast dynamic response of 2 s for a period for more than 6 months without significant change in the electrodes parameters.

Accuracy and precision of the potentiometric method: The accuracy and precision of the proposed method was determined at three concentration levels of GEMI by apply three replicate samples of each concentration. The standard deviations for the results did not exceed 2% are listed in Table 2, indicating high reproducibility of the results and precision of the method. This good level of precision was suitable for quality control analysis of GEMI and in the pharmaceutical formulations.

Robustness of potentiometric method for GEMI: Robustness was examined by evaluating the influence of small variation in the method variables on its analytical performance. In these experiments, one parameter was changed, whereas the others were kept unchanged, and the recovery percentage was calculated each time. It was found that small variables did not significantly affect the procedures, recovery values were shown in Table 3.

Analysis of pharmaceutical formulations: Proposed methods were applied to the pharmaceutical formulations and indicate the high accuracy of the proposed method for determination of GEMI. The proposed method has advantage of being virtually free from interferences by excipients. The percentage was 106.43 ± 0.51.

Recovery study of the potentiometric method: To a fixed amount of the drug in the dosage form and pure drug (the standard) were added at five different levels and the total was found by the proposed method each test was performed in triplicate. Table 4 revealing good accuracy and no interference from excipients. Recovery was calculated as the amount found/amount taken × 100. values are mean ± R.S.D. for three determinations.

The sensitivity: The sensitivity was tested by adding some inorganic salts and diluted acids and bases, it was found that the electrode shows excellent sensitivity toward testing species with RSD less than 2%.

Reproducibility: The electrode response shows excellent repeatability during analysis and very stable response with intraday RSD did not exceeded 2%, and inters day analysis with RSD less than 5%.

Conclusion

It can be concluded that GEMI-ZnO-ISE offers a viable technique for the direct determination of GEMI in pharmaceutical preparations. The sensor allows simple, rapid, and reproducible determination over a wide linear range of concentration with the same sensitivity without the need of complex sample manipulations. The sensor exhibits a good selectivity towards the drug in the presence of various pharmaceutical recipients, long life time and time-labor saving.

The procedure avoid the usual pretreatment steps necessary for GEMI assays and presents some general advantages over common chromatographic and spectroscopic procedure, it makes use of less sophisticated equipments (there for being easier to operate and providing lower cost of analysis) and surpasses color and turbidity problems associated with suspensions and colloids.

Sensor accomplished LOD and LOQ of 0.15 μM, 0.4546 μM, respectively with a fast response time of less than 5 seconds.

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