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Electrocatalytic Determination of Anti-Cancer Drug Imatinib, Using Ni Nanoparticle Modified Carbon Paste Electrode

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Abstract

In this research, nickel nanoparticles were synthesized by non-aqueous polyol method and morphology of nanoparticles was studied using scanning electron microscopy. Then Ni nanoparticle modified carbon paste electrode was prepared. Electrochemical behavior of modified electrode was studied in basic solution, using cyclic voltammetry and chronoamperometry methods. A pair of oxidation-reduction peaks relating to $Ni(OH)_2$/ NiOOH redox couple was observed in cyclic voltammogram of this electrode. Also, the electrochemical behavior of this electrode in presence of imatinib drug was studied. Results show that this modified electrode has a good ability for electrocatalytic oxidation of imatinib in basic solution. In presence of imatinib, current intensity of oxidation peak of electrode was increased, depending on its concentration. Linear dynamic range, limit of detection and rate constant of electrocatalytic reaction were determined using cyclic voltammetry and chronoamperometry methods. Amount of limit of detection (LOD) in cyclic voltammetry and hydrodynamic amperometry methods were calculated 1.2×10^{-6} M and 3.5×10^{-7} M respectively. Finally, the proposed sensor was successfully applied for determination of imatinib in real samples such as tablet and human blood plasma.

Keywords: Electrocatalytic oxidation, Nickel nanoparticles, Non-aqueous polyol method, Imatinib.

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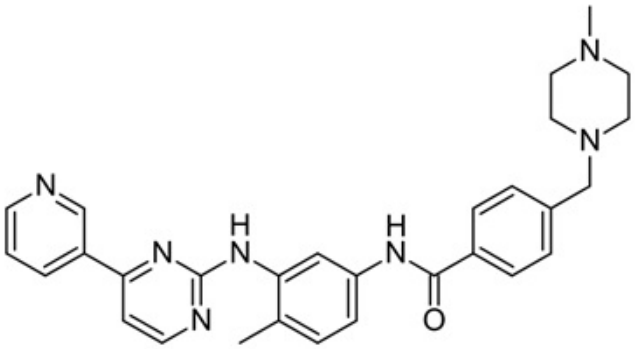
Introduction

Imatinib (Scheme. 1), with commercial name ofGlivec, is a medication used to treatcancer[1].The U.S.Food and Drug Administration (FDA) has approved imatinib as the first-line treatment forPhiladelphia chromosome-positive CML, both in adults and children [2].



Scheme. 1. Chemical structure of imatinib.

The commonly employed techniques for determination of this drug in bulk form, pharmaceutical formulations, and biological fluids such as blood plasma and urine, are based on spectroscopy [3,4] and HPLC [5-7] methods.The problems encountered using such methods are the need for time-consuming extraction procedures and expensive instrumentation, so the use of a simpler, faster, inexpensivebut sensitive electrochemical techniques can be an interesting alternative, especially those based on electroanalytical techniques. Electrochemistry has many advantages, making it an appealing choice for pharmaceutical analysis [8, 9]. Electrochemistry has always provided analytical techniques characterized by instrumental simplicity, moderate cost, and portability.Most of voltammetric determination of imatinibe was reported on mercury drop electrode and based on its reduction, which because of toxicity of Hg and needing to deoxygenation of analyte solution, is not favorable [10-13]. Also determination of imatinib based on its oxidation, was reported on the surface of some modified electrodes [14-16], e.g. by Brycht and coworkers [14] using a boron doped diamond electrode (BDDE). This electrode doesn't have the toxicity problem of mercury drop electrode, but before each determination,the surface of this electrode needs anodic activation in argon atmosphere.

On the other hand, the usefulness of modified carbon paste electrodes (MCPEs) in the electroanalytical chemistry has been widely demonstrated and their development for analysis applications is still of great interest [17]. Nowadays, it is important to develop new materials capable to change the electrode surface with better analytical properties, including graphene, nanoparticles, and carbon nanotubes [18, 19]. Among them, nanosized metal particle modified

electrodes have emerged as a promising alternative for the electroanalysis of organic and inorganic compounds [20, 21].

Electrochemical studies show that nickel nanoparticles can enhance electrode conductivity and surface area, facilitate the electron transfer, increse electroactive surface area and improve the detection limit of analyte [22–25]. These properties make it as a candidate for sensor application. Previously we reported elctrocatalytic oxidation and determination of carbohydrates [26, 27] and some antibiotic drugs [28] on Nickel/polymeric modified carbon paste electrodes. In this work, we decided to use the above-mentioned advantageous properties of the Ni nanopatricle modified electrode for the aim of electrocatalytic oxidation of imatinib as an anticancer drug. In this context, at first nickel nanoparticles was synthesized then mixed with graphite powder to construct the Ni-NP/MCPE (Nickel nanopartice/modified carbon paste electrode). Efficiency of this electrode as a sensor for the electrocatalytic oxidation and consequently determination of imatinib drug in alkaline media were investigated.

Experimental

Reagents and materials

All chemicals used in this experiment were analytical grade and used as received without further purifying. The solvent used in this work was twice distilled water. Graphite powder (particle diameter: 0.10 mm) and high purity paraffin oil (density: 0.88 g cm^{-3}),were purchased from Fluka. Nickel chloride hexahydrate ($NiCl_2$. $6H_2O$), 80 wt% hydrazine hydrate (N_2H_4. H_2O), ethylene glycol (EG) and sodium hydroxide (NaOH) were obtained from Merck.

Synthesis of nickel nanoparticle

Nickel nanoparticles were synthesized by process reported in reference [29]. In this process which called polyol and has been widely used by many research groups to synthesize metal particles, ethylene glycol acts as a solvent.In a typical experiment, 60 mL of 0.15 M $NiCl_2$. $6H_20$, 30 mL of 0.15 M$N_2H_4$and 10 mL of 1 M NaOH were mixed in a three-neck flask equipped with stirring bar, a thermometer, a dropping funnel and a condenser. All the reactants were diluted and dissolved in EG to form above mentioned concentration. Hydrazine was first heated to boiling point of the mixture, which was about 184°C. A mixture of $Ni^{2+}$and appropriate amount of NaOH was added quickly into the heated hydrazine when it reached the boiling point. The temperature was maintained at a constant value at the boiling temperature of mixture that was controlled using oil-bath. Initially the green solution turned into black, indicating the formation of Ni metal. The mixture was heated for

30 min under strong stirring. After the reaction was completed the colloidal was cooled to room temperature and the particles were precipitated from the solution by adding ethanol.

Preparation of working electrode

A mixture of graphite powder and paraffin oil was blended by hand mixing with a mortar and pestle for preparation of carbon paste. The resulting paste was then inserted in the end of a glass tube (internal radius: 2 mm) with a copper wire for electrical connection. A new electrode surface was quickly made by removing a small plug of the paste with a stainless steel rod and smoothing the resulting surface on white paper until a smooth shiny surface was observed. A modified paste was prepared in the same way, except that the graphite powder was mixed with 1 percent of nickel nanoparticles.

Instrumentation

The electrochemical experiments were carried out using a potentiostat/galvanostat (Sama 500-C Electrochemical Analysis System, Sama, Iran). The three-electrode system consist of the modified carbon paste electrode as working electrode, Ag|AgCl|KCl (3 M) as a reference electrode and a Pt wire as a counter electrode were used in this system.

Preparation of a real sample

For analysis of the imatinib tablets, the average mass of three tablets was calculated. The tablets were finely powdered and homogenized in a mortar. An appropriate, accurately-weighted amount of the homogenized powder was transferred to a standard 100 ml flask containing 50 ml of 0.1 M sodium hydroxide solution. The contents of flask were sonicated for 15 min; the undissolved excipients were removed by centrifuge and then diluted to volume with the same supporting electrolyte. Appropriate solutions were prepared by taking appropriate aliquots of the clear filtrate and diluting them with 0.1 M sodium hydroxide solution.

Results and discussion

Scanningelectron microscopy (SEM)

Figure 1 shows SEM image of Ni nanoparticles, indicates that these particles were formed well with an average size of 50 nm.

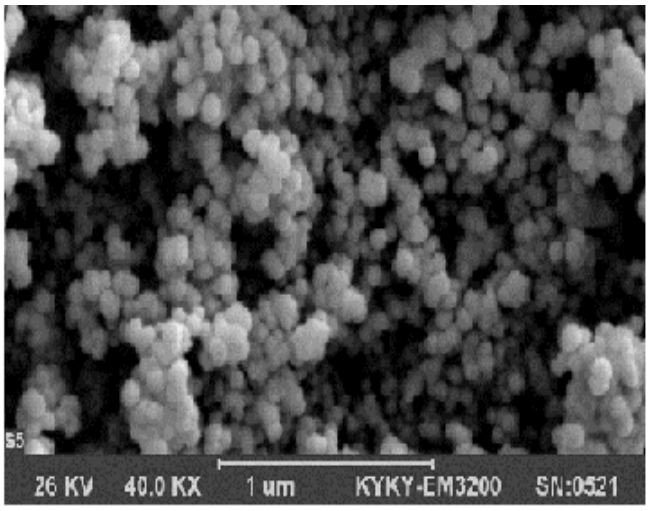


Figure 1. SEM image of Ni nanoparticles.

Electrochemical behavior of the Ni-NP/MCPE

The polarization behavior of Ni-NP/MCPE was tested in 0.1 M NaOH using cyclic voltammetry. This technique allows the oxide film formation in parallel to inspecting the electrochemical reactivity of the surface. Voltammograms were recorded by cycling the potential between 0.1 and 0.7 V at 100 mV s^{-1} until a stable voltammogram was obtained. Fig. 2 shows the electrochemical response of the CPE and Ni-NP/MCPE after polarization in 0.1 M NaOH solution.

From Figure 2**,** it can be seen that whereas neither oxidation nor reduction took place on the CPE, a well-developed redox wave was observed on the Ni-NP/MCPE when the potential was swept and cycled between 0.1 and 0.7 V, which was related to the oxidation of $Ni(OH)_2$ to NiOOH with a peak potential of 0.46 V and reduction of NiOOH to $Ni(OH)_2$ with a peak potential of 0.33 V (equation 1).

$$Ni(OH)_2 + OH^- \longleftrightarrow NiOOH + H_2O + e^- \quad (1)$$

An approximate estimate of amount of incorporated Ni(II) on Ni-NP/MCPE (surface coverage of the electrode) can be evaluated using equation $\Gamma^* = Q/nFA$, where Q is the electric charge obtained by integrating anodic peak obtained at 10 mV s^{-1} (Figure 2b), with the background correction; n, F and A present the number of electrons transferred in redox reaction, faraday constant and geometric electrode area, respectively. According to internal radius of glass tube, $A= \pi r^2$ is equal to 0.1256 cm^2. The value of Γ^* for Ni-NP/MCPE was 7.6×10^{-6} mol cm^{-2}.

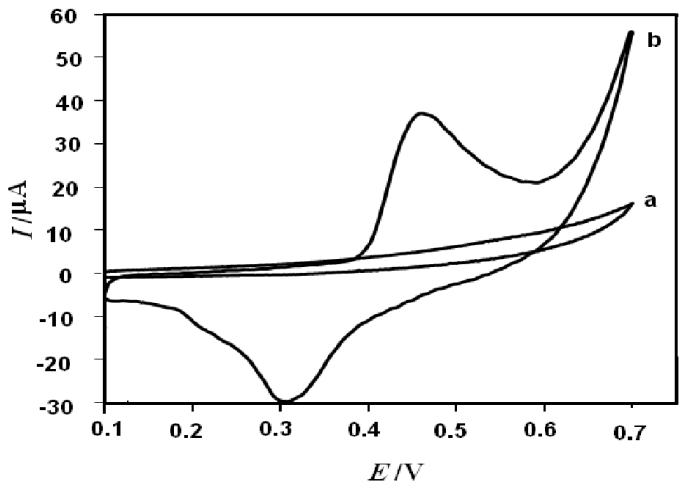


Figure 2. Electrochemical responses of a) CPE and b) Ni-NP/MCPE, in 0.1 M NaOH solution, scan rate 10 mVs^{-1}.

Electrocatalytic oxidations of imatinib on the surface of Ni-NP/MCPE

Cyclic voltammetry studies

In this work, the oxidation of imatinib was first studied at a bare CPE (without nickel nanoparticles) by cyclic voltammetric experiments in 0.1 M NaOH solution. Typical results obtained for a potential range from 0.1 to 0.6 V vs. Ag|AgCl|KCl (3 M) at potential scan rate of 10 mV s^{-1} is shown in Figure 3. Response of CPE in the absence of imatinib is shown in Fig. 3 a; the addition of 0.1 mM imatinib to the alkaline solution causes no effect on the electrochemical response of the CPE (Fig. 3b). The electrochemical response of the Ni-NP/MCPE in 0.1 M NaOH solution exhibits well defined anodic and cathodic peaks (Fig. 3c) related to the Ni(II)/Ni(III) redox couple. As it is seen in Figure 3d, after adding 0.1 mM imatinib there is an increase in the anodic peak current and a decrease in the cathodic peak current. This behavior is typical of that expected for the mediated oxidation (EC′ mechanism) as follows:

$$Ni(OH)_2 + OH^- \longleftrightarrow NiOOH + H_2O + e^- \qquad E \qquad (2)$$

$$NiOOH + \text{imatinib} \longrightarrow Ni(OH)_2 + \text{Product} \qquad C' \qquad (3)$$

Thus modifier layer of $Ni(OH)_2$ at electrode surface acts as a catalyst for oxidation of imatinib in NaOH solution.

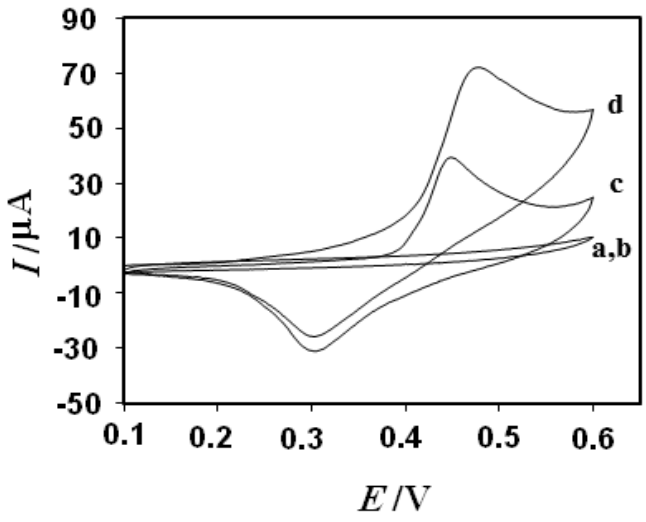


Figure 3. Electrochemical responses of CPE to a) 0, b) 0.1 mM imatinib and Ni-NP/MCPE to c) 0 and d) 0.1 mM imatinib in 0.1 M NaOH solution, scan rate 10 mV s^{-1}.

Chronoamperometric studies

Chronoamperometry, as well as other electrochemical methods, were employed for the investigation of electrode processes at chemically modified electrode. The main panel of Figure 4 shows chronoamperometric measurements of imatinib at the Ni-NP/MCPE. These current–time profiles obtained by setting the working electrode at first potential step of 550 mV and second potential step of 300 mV for various concentrations of imatinib. The forward and backward potential step chronoamperometry of the modified electrode in the blank solution showed an almost symmetrical chronoamperogram with almost equal charges consumed for the oxidation and reduction of surface confined Ni (II)/Ni (III) sites. However, in the presence of imatinib, the charge value, Q, associated with the forward chronoamperometry is greater than that observed for the backward chronoamperometry (Inset (A) of Fig. 4). The rate constant for the chemical reaction between the imatinib and redox sites of Ni-NP/MCPE, can be evaluated by the chronoamperometry according to the method described in the literature [30].

$$I_C/I_L = \gamma^{1/2}[\pi^{1/2}\,\mathrm{erf}\,(\gamma^{1/2}) + \exp(-\gamma)/\gamma^{1/2}] \qquad (4)$$

Where I_C is the catalytic current of the Ni-NP/MCPE in the presence of imatinib, I_L is the limiting current in the absence of imatinib and $\gamma = kc_o t$ (c_o is the bulk concentration of imatinib) is the argument of the error function. This equation can be used to define the limiting regions of behaviorfor all EC' mechanism. For small values of γ (e.g., $\gamma < 0.05$), $\mathrm{erf}(\gamma^{1/2}) \approx 2\gamma^{1/2}/\pi^{1/2}$ and $I_C/I_L \approx 1$ (diffusion pure region); here the catalytic reaction has no effect. For $\gamma > 1.5$, $\mathrm{erf}(\gamma^{1/2}) \rightarrow 1$, $\exp(-\gamma)/\gamma^{1/2} \rightarrow 0$, and equation can be reduced to:

$$I_C/I_L = \gamma^{1/2}\pi^{1/2} = \pi^{1/2}\,(kc_o t)^{1/2} \qquad (5)$$

This defines the kinetic pure region (KP), in which $I_C/I_L>2.17$. In this region the chronoamperometric response can be employed to determine γ (or $kc_o t$). Where k, c_o and t are the catalytic rate constant (cm^3 mol^{-1} s^{-1}), imatinib concentration (mol cm^{-3}) and time elapsed (s), respectively. From the slope of the I_C/I_L vs.$t^{1/2}$ plot we can simply calculate the value of k for a given concentration of substrate. Inset (B) of Figure 4 shows one such plot, constructed from the chronoamperogram of the Ni-NP/MCPE in the absence and presence of 0.2 mM imatinib.The mean value for (*k*) were found to be 1.6×10^7 cm^3 mol^{-1} s^{-1}.

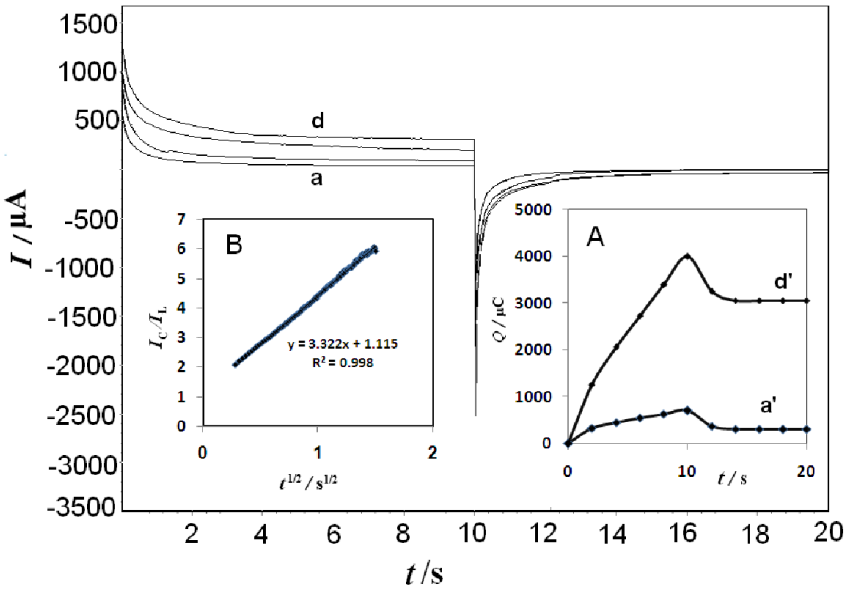


Figure 4. Main panel)Chronoamperograms obtained at the Ni-NP/MCPE in the absence (a) and presence of 0.025(b), 0.12 (c) and (d) 0.2 mMof imatinib in 0.1 M NaOH solution, first and second potential steps were 0.55 and 0.30 V. inset A) Dependence of *Q* (μC) vs. *t*, (a') and (d') respectively derived from the data of chronoamperograms (a) and (e) Inset B). Dependence of I_C/I_L on $t^{1/2}$ derived from the data of chronoamperogams of (a) and (e).

Calibration plot and limit of detection

Figure 5(A) shows the cyclic voltammograms of the Ni-NP/MCPE in the presence of different concentration of imatinib. As can be seen Ni-NP/MCPE exhibits a well-defined catalytic oxidation current increasing linearly with increase in imatinib concentration. Calibration plots for analysis of imatinib show linear dependence of the anodic peak current on imatinib concentration in solution (Figure 5(B)), in the linear range of 0.004 to 0.4 mM and a correlation coefficient of 0.992. The detection limit, taken as the concentration that gave a signal equal to three times the standard deviation of the blank signal, calculated from the calibration graph, was 1.2 μM.

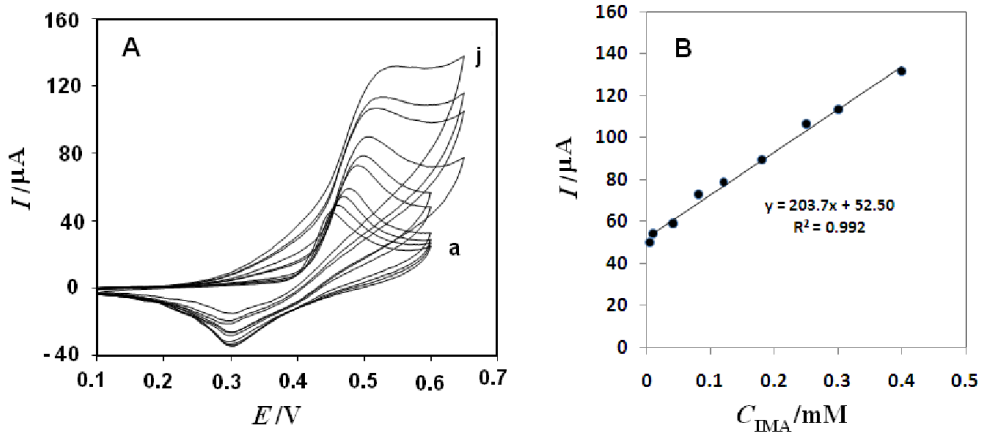


Figure 5. A) Current–potential curves for oxidation of imatinib at the Ni-NP/MCPE in 0.1 M NaOH solution with different concentrations of imatinib: a) 0, b) 0.004, c) 0.01, d) 0.04, e) 0.08, f) 0.12, g) 0.18, h) 0.25, i) 0.3 and j) 0.4 mM. B) Plot of Ip versus imatinib concentration.

Since the cyclic voltammmetry is not sensitive for low concentrations measurements, the amperometry under stirred conditions was employed instead of cyclic voltammetry.Figure 6(A) show typical current–time responses for the successive addition of 0.1 mL from 0.05 mM imatinib standard solutions, to 10 mL electrolyte solution. As shown in the figure a well defined response was observed during the successive addition of imatinib solutions. It was observed that the sensor responds so rapidly to the substrate, as, about 95% of the steady-state current is obtained within 4 s. Figure 6 (B) is the plots of catalytic current which is changed linearly with the imatinib concentration in the range 1 µM to 38 µM. The detection limit is 0.35 µM.

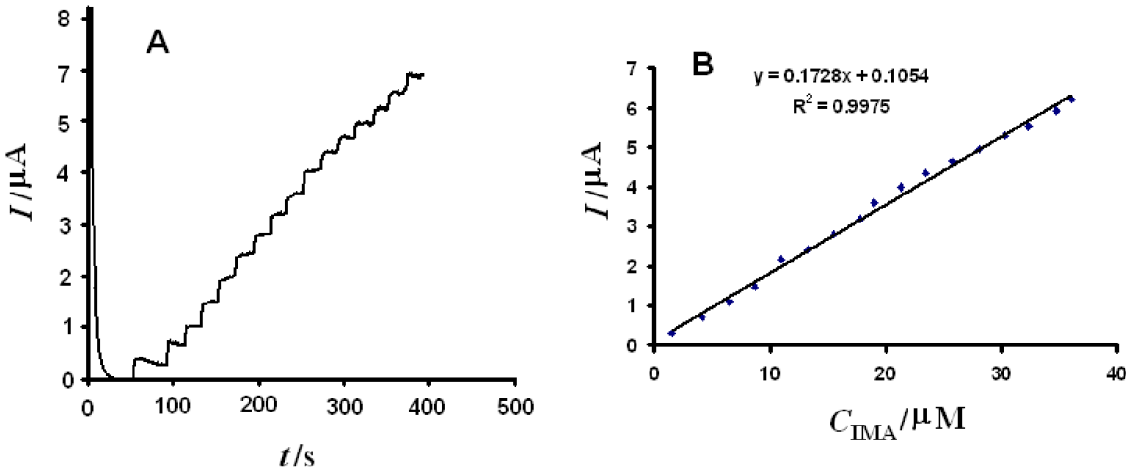


Figure 6. A) Typical amperograms showing the current response for successive added volumes of 0.05 mM solution of imatinib in 0.1 M NaOH solution. B) Variation of amperometric current vs. imatinib concentration.

The reproducibility of the modified electrode preparation and its use for imatinib sensing is expressed in terms of relative standard deviation (RSD), which is found to be 3.5 % at imatinib concentration of 0.2 mM for five electrodes. The repeatability of the Ni-NP/MCPE was investigated by performing four determinations using a single electrode with the same imatinib solution (0.2 mM). The RSD for these determinations was found to be 5%.

Determination of imatinib in a real sample

To illustrate the modified electrode application in practical analysis, it was used to detect imatinib in human plasma and drug tablet samples. All samples were diluted with 0.1 M NaOH solution and a known amount of imatinib was spiked to plasma solution. Then standard addition method was used to analyze the prepared samples. The quantity of experimentally determined imatinib was compared to that of reported and spiked values, respectively in tablet and plasma samples. For comparison, a different method based on spectrophotometric determination [31] was used for drug sample. The t and F-test values refer to comparison of the proposed method with the reference method. The calculated t and F values are less than the theoretical values at 95% confidence level, which show precision and accuracy of proposed method. The results are summarized in Table 1.

Table. 1. Results of determination of imatinib using Ni-NP/MCPE (n = 5, P = 0.05).

Sample	Amount labeled	Amount added	Found by proposed method*	Found by Spectroscopy method	Recovery(%)
Plasma	------	10 μM	10.3 ± 0.14 μM	----------	103
Plasma	-------	30 μM	30.5 ± 0.45 μM	----------	101.7
Tablet	100 mg	-------	108 ± 2.32 mg F = 1.26, t =1.80	105± 2.92	--------

*Average ± standard deviation. Theoretical values at 95% confidence level, F = 6.39, t = 2.78.

The analytical performance of the proposed electrode for the determination of imatinib has been compared with some of the previously reported techniques listed in Table 2. It can be seen that although our reported method has higher limit of detection respect to the reported methods, but its linear range is most better than most of other methods. moreover, this proposed sensor doesn't need expensive instrumentation respect to chromatography and fluorescence techniques; also preparation of Ni/NP/MCPE is simple, low cost and doesn't have toxicity problem of mercury drop electrodes. Also one of disadvantages of stripping methods is long analysis time, because before each voltammetric measurement a long time is need for adsorption of analyt on the electrode surface, therefore the proposed method is a time saving alternative.

Table. 2. Comparison of proposed method with some of reported works for determination of imatinib.

Technique	Detection method	Electrode	Linear range (M)	LOD (M)	Ref
Electrochemical	AdSV	HMDE	1×10^{-8} - 4.8×10^{-7}	5.2×10^{-9}	12
Electrochemical	AdSV	HMDE	9×10^{-9} - 3×10^{-8}	2.6×10^{-10}	10
Electrochemical	DPV	BDDE	3×10^{-8} - 2.5×10^{-7}	2.1×10^{-8}	14
Electrochemical	DPV	Fe_3O_4@MWCNTs@PANNFs/CPE	1.7×10^{-9} - 8.5×10^{-7}	4×10^{-10}	15
Electrochemical	SWV	MWCNT-COOH	5×10^{-8} - 9.1×10^{-7}	7×10^{-9}	16
Electrochemical	Potentiometry	PVC-membrane	1×10^{-5} - 1×10^{-3}	1.1×10^{-6}	32
Chromatography	LC-MS/MS	----	1×10^{-7} - 7.1×10^{-6}	1×10^{-7}	33
Fluorescence	Quenching	----	2×10^{-5} - 8.1×10^{-4}	4.9×10^{-9}	34
Electrochemical	CV	Ni-NP/MCPE	4×10^{-6} - 4×10^{-4}	1.2×10^{-6}	This work
	HA		1×10^{-6} – 3.8×10^{-5}	3.5×10^{-7}	

HMDE: Hanging mercury drop electrode
AdSV: Adsorptive stripping voltammetry
DPV: Differential pulse voltammetry
SWV: Square wave voltammetry
CV: Cyclic voltammetry
HA: Hydrodynamic amperrometry
LC-MS/MS :Liquid chromatography-tandem mass spectrometry

Conclusion

This study illustrated a novel carbon paste electrode modified with Ni nanoparticles that can be successfully used for the determination of imatinib, as an important anticancer drug; and a good linear dynamic range and acceptable detection limit was obtained.This proposed method has many advantages including: low cost of reagents and apparatus, easy and simple preparation process, time saving and reproducibility; also the proposed method is applicable for determination of imatinib with good accuracy in biological media and pharmaceutical formulations.

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