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Review

Carbon based nanomaterials for the detection of narrow therapeutic index pharmaceuticals

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ABSTRACT

Precise detection of important pharmaceuticals with narrow therapeutic index (NTI) is very critical as there is a small window between their effective dose and the doses at which the adverse reactions are very likely to appear. Regarding the fact that various pharmacokinetics will be plausible while considering pharmacogenetic factors and also differences between generic and brand name drugs, accurate detection of NTI will be more important. Current routine analytical techniques suffer from many drawbacks while using novel biosensors can bring up many advantages including fast detection, accuracy, low cost with simple and repeatable measurements. Recently the well-known carbon Nano-allotropes including carbon nanotubes and graphenes have been widely used for development of different Nano-biosensors for a diverse list of analytes because of their great physiochemical features such as high tensile strength, ultra-light weight, unique electronic construction, high thermochemical stability, and an appropriate capacity for electron transfer. Because of these exceptional properties, scientists have developed an immense interest in these nanomaterials. In this case, there are important reports to show the effective Nano-carbon based biosensors in the detection of NTI drugs and the present review will critically summarize the available data in this field.

1. Narrow therapeutic index pharmaceuticals

Narrow therapeutic index (NTI) pharmaceuticals is a subject that may be minimally well-known to very clinicians; although, it has significant implication for the care of patients, especially with regard to controlling oral anticoagulation. NTI pharmaceuticals (also known as critical dose drugs) are FDA-designated (Food and Drug Administration) agents for which small alterations in systemic concentration can result in important alterations in pharmacodynamic feedback. Too much or too little of NTI pharmaceuticals may lead to either toxic impact or inefficient cure of the patient's state. The name narrow therapeutic index pharmaceuticals should intensify our sensitivity as scientists and clinicians [1]. The TI (therapeutic index, also known as therapeutic window) of a pharmaceutical is described as the ratio of LD_{50} (lethal drug dose in 50% of subjects) to the ED_{50} (effective drug dose in 50% of subjects). ($TI = \frac{LD50}{ED50}$). Whatever the TI is larger, then the drug is safer and in fact, there is less possibility to see the adverse drug reactions if the usual drug dosages have surpassed. Many of the drugs have good TI (10 or above) and therefore the clinicians are not worried about the serious toxicity reactions. However for NTI drugs (almost with TI of 2 or less), the therapeutic range is very narrow and a simple fault in dosage calculation and further monitoring can lead to life-threatening reactions [2].

The FDA has recognized approximately 25 narrow therapeutic index pharmaceuticals. Some of the generally identified narrow therapeutic index pharmaceuticals are Digoxin, Warfarin, Carbamazepine,

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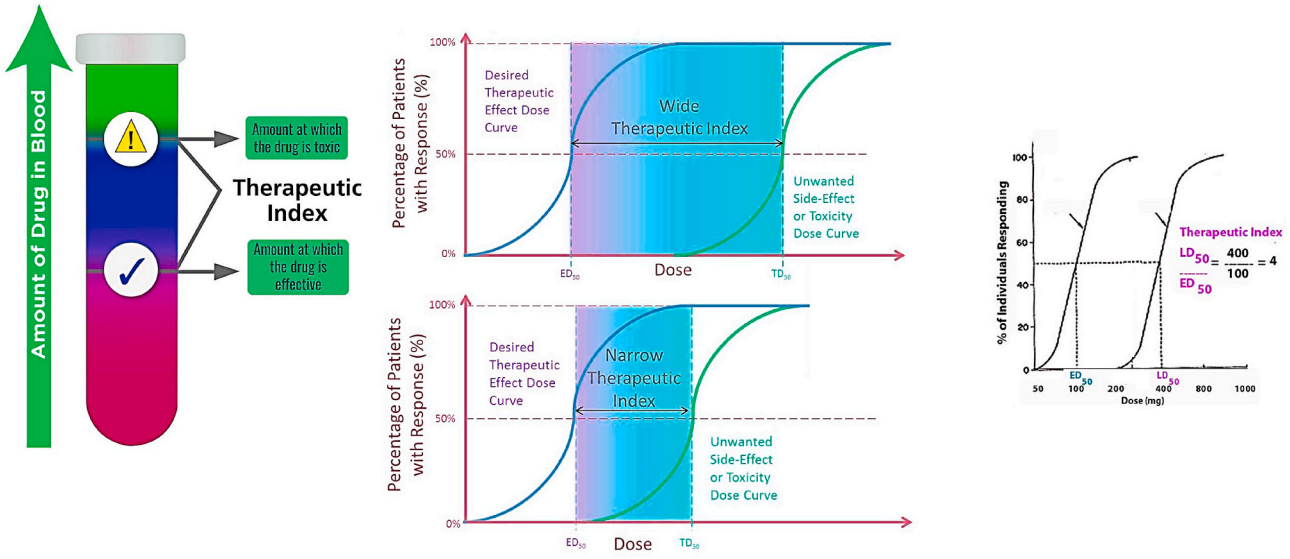
Phenytoxin, phenobarbital, Theophylline, Levothyroxine (T4) and etc., used in crucial therapies. These pharmaceuticals have association with toxic reactions, high risks and major drug-drug interactions [3,4]. Narrow therapeutic index pharmaceuticals need greatly individualized dosing, near patient controlling and evaluation to keep their safety and profit. The possible peril for most of narrow therapeutic index pharmaceuticals is combined by the fact that optimum dosage differs for each sick person. The same dosage of an NTI pharmaceutical for one person can create a completely dissimilar consequence in another [3]. There are numerous effective but greatly toxic pharmaceuticals that demonstrate an NTI and show variable interpatient pharmacokinetics. Individualized treatment with such pharmaceuticals needs precise TDM (therapeutic drug monitoring) to get the hoped clinical outcomes safely [5]. TDM, in which monitoring of specific drug is measured in time intervals to maintain a constant concentration, is mostly important for narrow therapeutic index drugs [6].

As mentioned above some of the narrow therapeutic index pharmaceuticals are such as Carbamazepine, Digoxin, Phenytoin, phenobarbital, Warfarin, Theophylline and Levothyroxine (T4) employed in vital therapies and it is important to accurately control their amount in the body due to their narrow therapeutic index. As an iminostilbene derivative, carbamazepine applied as the first choice drug for trigeminal neuralgia treatment and also for both partial and generalized seizures for more than 3 decades, because of quick monitoring of extreme electrical discharges of cerebral and the low incidence of chronic and acute toxicity [7]. The most common cardiac glycoside is digoxin utilized in the treatment of various heart conditions like congestive heart failure and atrial fibrillation. Currently, it is employed as an antiarrhythmic drug and is usually prescribed to lessen the ventricular rate at the time of existing of flutter and atrial fibrillation and also to boost the sufficiency of circulation in congestive heart failure patients [8,9]. As a rodenticide, warfarin is an anticoagulant which inhibits the synthesis of coagulation factors dependent on vitamin K. Due to the very narrow therapeutic index of warfarin, accurate and precise monitoring of its amount in the blood is required [10]. As a methyl xanthine derivative, theophylline is plentiful in nature. It is classified as one of significant natural alkaloids found in vast amount of cocoa beans, tea and coffee. Theophylline serves the nonselective antagonist role for adenosine receptor. It is effective in the respiratory diseases treatment and prescribed for therapy of chronic obstructive pulmonary disorder and asthma [11,12]. Phenytoin and phenobarbital are antiepileptic drugs used in poly and monotherapy in the treatment of psychological and epilepsyScheme 1 conditions such as post-traumatic stress, anxiety, autism, and depression disorders [13].

2. Conventional methods for determination of narrow therapeutic index drugs

Techniques for detecting drugs include chemical and visual analysis. Factors involved in packaging and drugs can be utilized for visual analysis. A number of chemical analysis techniques (analytical methods) developed for determination of narrow therapeutic index drugs include spectroscopy methods (near-infrared spectroscopy (NIRS), near infrared chemical imaging (NIR-CI), Raman spectroscopy, X-ray fluorescence (XRF), powder X-ray diffraction (PXRD), infrared spectroscopy), chromatography methods (HPLC), mass spectrometry (Isotope Ratio Mass Spectrometry, Ion Mobility Mass Spectrometry, Ion Mobility Spectrometry (IMS)), GC-MS method. Nevertheless, some of these analytical techniques are not specific and are time-consuming [14]. Actually, laboratories for drug testing advanced their assay strategies employing different analytical techniques such as HPLC (high-performance liquid chromatography). However, the majority of used drug assays in the laboratories are some alternative of immune-binding assay processes which are commercially available [15]. The most widely employed procedures are ELISA (Enzyme-Linked Immunosorbant Assay), EMIT (Enzyme MultipliedImmunoassay Technique) and FPIA (Fluorescence Polarization Immunoassay) [16,17]. However, much number of these currently utilized techniques are time-consuming, expensive, and laborious, required more sophisticated and complicated instruments and experimental procedures, highly costly and also suffer from low sensitivity and selectivity (Table 1). When it comes to biosensors, most of the above problems could be solved straight away. The development of biosensors has demonstrated that a broad variety of economic and simple analysis can become possible. Simplicity, rapidity, high sensitivity and low cost are the promising features of biosensors for analysis of biological compounds [18–20]. Recently, experts in various medical fields, from diagnostic to therapeutic, have turned their attention towards nanoparticles and nanotechnology to improve the above-mentioned parameters and boost the quality of the materials to resolve the problems faced using conventional compounds [21,22]. The main goal of this review is to introduce novel carbon nanomaterial-based nano-biosensors for the determination of narrow therapeutic index pharmaceuticals.



Scheme 1. Therapeutic Index, Dose response curve for wide and narrow therapeutic index medications.

Table 1
Features of instrumental analytical technologies [14,23].

Analytical technique	Testing method	Description	Characters	Cost	Need reference standards or not	Need instrument or not	Need database or not
Chromatography	HPLC	By establishing the database of UV spectra of analytes and the retention Factors, to qualitatively and quantitatively detect the ingredients and target compounds.	Rapid, high sensitive, High performance, high pressure, applying widely, both for qualitative and quantitative determination. High investment, complex Research. Instruments are accessible on the market	High	Yes	Yes	Yes
Chromatography	Capillary Electrophoresis (CE) technique	In CE technique a capillary tube utilized as a separating channel, and as motive power high voltage direct current field. It has different kinds of separation. It could both qualitatively and quantitatively detect the target compounds rapidly.	Low Cost, rapid, high performance. High investment, complexed research.	High	Yes	Yes	No
Spectroscopy	Near-infrared (NIR) Spectroscopy	The technique is based on mixture vibrations of hydrogen (H) groups like NH, CH and OH from about 800 to 2500 nm and molecular overtone.	High performance, rapid, low cost, nondestructive, easy, accurate, without need for chemical reagents, use for both qualitative and quantitative determination. High investment and complexed research. Instruments are accessible on the market	High	No	Yes	Yes
Spectroscopy	Mid-Infrared (MIR) Spectroscopy	The method, about 4000–400 cm^{-1} (2.5–25 μm) is utilized to study related rotational-vibrational structure and the fundamental vibrations.	Rapid, high performance, easy, nondestructive, low cost, accurate, without need for chemical reagents, utilize for both qualitative and quantitative determination.High investment and complexed research. Instruments are accessible on the market	High	No	Yes	Yes

3. Carbon nanomaterials and their applications in nano-biosensors

Usage of nanomaterials for biosensors development has been generated a great deal of interest, and carbon nanomaterials (CNMs) are at the forefront of this attention. Carbon nanomaterials comprised of sp2 linked graphitic carbon, are mainly categorized into fullerenes (zero-dimensional), carbon nanotubes (one-dimensional), and graphene (two-dimensional). The characteristics of carbon nanomaterials are vigorously dependent on their interactions with different materials and atomic structures [24–27]. The distinctive structure of these nanomaterials permits them to non-covalently interact with organic molecules via different forces like π-π stacking, hydrogen bonding, hydrophobic interactions, van der Waals and electrostatic forces. These interactions and their nano-sized, layered or hollow structures lead them to be good candidates in various analytical applications [28]. Moreover, carbon nanomaterials have found great potentials in multiple aspects of biomedicine including bio-sensing, targeted drug and gene delivery, tissue and cell imaging, antibacterial actions, cancer therapy and regenerative medicine [29–36]. While using carbon nanostructures in the mentioned areas of nanomedicine have been associated with increased risk of toxicity, many reports have shown that proper functionalization can led to the reduction of toxicity risks [37–39]. Furthermore, carbon nanomaterials are able to combine with a variety of nanomaterials to generate nanocomposites with different features in a single new material, such as fullerene-Pd nanocrystals, ceramic-CNTs (carbon nanotubes), Teflon-CNTs, and etc.

Carbon nanomaterials can lead to the generation of significant advancements in all analytical applications step. They have a wide range of applications in nanoelectronics, mechanical engineering and biomedicine [28,40]. Recently, carbon nanomaterials and electrodes based on these nanomaterials have demonstrated the important electrocatalytic capabilities. Approaches to construct carbon nanomaterial based biological sensors involve functionalizing material surface with carbon nanomaterials, synchronously depositing metal nanoparticles with carbon nanomaterials, doping these nanomaterials into polymers, or utilizing them to enhance conductivity [41]. Generally, carbon nanomaterials application in analytical chemistry is beneficial. While appropriately selected, these novel nanomaterials are potentially able to produce vital enhancements in all of the analytical procedures: preparation of specimen, separation and determination [28].

Carbon nanomaterials based nano-biosensors are usually utilized due to their biocompatibility, great kinetics of electron transfer, low cost, and great chemical stability. Conventional sensors based on carbon contain GCE (glassy carbon electrodes), pyrolytic graphite or carbon fibers. Currently, carbon nanomaterials have been widely integrated into different biosensors. The size of 1–100 nm is a notable aspect of these nanomaterials and they are beneficial due to their special surface area and high surface-volume ratio. Moreover, these nanomaterials have improved properties of interfacial adsorption, the kinetics of rapid electron transfer, preferable electrocatalytic activity, and great biocompatibility in comparison to many conventional materials of sensors [40].

4. Application of carbon nanomaterials in the detection of narrow therapeutic index pharmaceuticals

Nanomaterials are potentially able to improve and accelerate the ultimate goals of medicine in terms of diagnosis and treatment. Carbon nanomaterials have been shown to be extremely advantageous category of nanomaterials, also they are broadly utilized in electrochemistry because of their low cost and broad potential range. More currently, enormous gains have been made toward the biomedical application of carbon nanomaterials from carbon dots and nanodiamonds to graphene, graphene quantum dots and carbon nanotubes [42–44]. The unique electrical, mechanical, optical, chemical and thermal properties of

carbon nanomaterials made them broadly utilized materials for a variety of applications involving biomedicine. CNMs have been incorporated in many novel biosensors as they are good electron transfer enhancers and in this regards there are considerable reports which showed their important role in the specific biosensors for NTI drugs. Herein, an overview of recent efforts to use carbon nanomaterials in nano-biosensors for the detection of a number of NTI pharmaceuticals such as digoxin, carbamazepine, warfarin, theophylline, phenytoin and phenobarbital are provided.

4.1. Digoxin

Around 200 years ago, digoxin (DX) has been made known in clinical operations which is a well-established drug for use in cardiovascular disease. It is the most usually utilized cardiac glycoside in treating various heart situations like congestive heart failure (CHF) and atrial fibrillation (AF) [8,45]. Currently, digoxin is recommended for heart rate management in AF patients, especially patients with concomitant heart failure (HF). The digoxin has been investigated in patients with sinus rhythms and HF, but there is not any randomized monitored trail for long term safety and efficacy of digoxin in AF suffered patients [46]. Digoxin has a narrow therapeutic index which is affected by important drug-drug interactions and may lead to harm unless thoughtfully administered involving typical measurements of serum levels of digoxin [45]. The concentration of digoxin in serum among the patients with HF is directly associated with mortality, low levels of digoxin (0.5–0.8 ng/ml) in patients lead to declined mortality whereas >1.1 ng/ml levels cause enhanced mortality [46]. Considering that the toxicity amount of digoxin in serum is 2 ng/ml, it is extremely monitored in the patient's blood in order to prevent toxicity [47]. The risk factors for toxicity of digoxin are renal failure, patient age, drug interaction and metabolic disorders [48]. Traditional techniques for digoxin determination in clinical specimens include ELISA (enzyme-linked immunosorbent assay), fluorescence, gas chromatography, mass spectrometry, high performance liquid chromatography with UV, and LC-MS/MS which requires complexed instruments [49–53]. However, biosensors possess important advantages like low-cost, great sensitivity, and are easy to use [54].

Lately, a very sensitive aptasensor was designed for detection of digoxin in biological specimens. Aptamers are short single stranded oligonucleotides capable of binding to target molecules with high specificity and affinity. Due to their catalytic and receptor properties, they also use as great bioreceptors for the detection of different analytes as the aptasensors platforms [55]. In this study, the gold nanoparticles (AuNPs) was employed for modification of gold screen printed electrode surface through electrodeposition. A monolayer of MPA (3-mercaptoperopionic acid) was attached to AuNPs modified electrode surface by self-assembly. Afterwards, amino-labeled aptamer which was specific for digoxin was covalently linked to the MPA carboxylic groups on the AuNPs via construction of imide bond.. The AgNPs/GO (silver nanoparticles decorated GO) had interaction with aptamer which was immobilized onto the surface of modified electrode through π-π interaction and oxidation signal of silver nanoparticles was controlled. In the existence of digoxin, digoxin-aptamer specific interaction caused to the release of hybrid from surface of electrode and the oxidation signal was reduced. The designed aptasensor demonstrated 1 pM-0.1 μM linear range with 0.3 pM limit of detection, also it was successfully applied for determination of digoxin in biological specimens with excellent reliability [56].

An electrochemical aptasensor was fabricated for diagnosis of digoxin based on FTO (fluorine-doped tin oxide) in which immobilization of thiolated-digoxin aptamer was occurred on the AuNPs deposited fluorine-doped tin oxide surface. The electrochemical aptasensor was based on a reduction of current of MB (methylene blue) after incubation with digoxin. The linear concentration range of digoxin with aptasensor was between 0.02 and 0.2 μg/L and LOD was 0.01 μg/L. The developed aptasensor successfully detected digoxin in plasma and urine samples [57].

In another study, a GSPE (gold screen printed electrode) surface was modified with electrodeposition of AuNPs as well as self-assembly of MPA on the AuNPs. Amino-labeled specific aptamer was linked to the surface of electrode through forming carbodiimide bond. Accumulation of GO on the surface occurred via interacting with aptamer aromatic nucleobases and the potassium ferriciyanide signal of reduction was declined. The immobilized graphene oxide was released from the electrode surface in the existence of digoxin which caused to an increment of current. The linear range of fabricated aptasensor was from 0.1 pM to 1.0 μM with 0.050 pM limit of detection (Fig. 1) [58].

Two new ultrasensitive fluorescent biosensors were developed for sensitive and fast detection of digoxin based on digoxin aptamer and rGQDs (reduced graphene quantum dots). Firstly, a label free aptamer had an interaction with rGQDs which led to increment of rGQDs fluorescence intensity. Addition of digoxin resulted in construction of digoxin-aptamer complex and decrease of fluorescence intensity. According to the results, the obtained detection limit was $29.87 \pm 1.01 \times 10^{-12}$ mol/L. Secondly, in order to enhance the sensitivity and reproducibility of biosensor, an amine-labeled aptamer was utilized. At first, fluorescence intensity of rGQDs-aptamer was turned-off employing oxidized CNTs (carbon nanotubes) by FRET (fluorescence resonance energy transfer) technique. Addition of digoxin and its interaction with amine labeled aptamer was resulted in inhibition of CNTs connection with rGQDs-aptamer, therefore, the rGQDs fluorescence was turned-on. The second strategy supplied fast, simple, low-cost, ultrasensitive with great reproducibility for detection of digoxin with limit of detection $7.95 \pm 0.22 \times 10^{-12}$ mol/L. Both of luminescent biosensors were well applied for quantification of digoxin in urine and serum with good results. Elmizadeh and et al. developed an ultrasensitive new fluorescent apta-nano-biosensor for sensitive and fast digoxin detection in biological fluids. For fabrication, they utilized digoxin aptamer as sensing material and rGQDs (reduced graphene quantum dots) as optical probe. Direct interaction of label-free aptamer with rGQDs was led to increment of rGQDs fluorescence intensity. Upon adding of digoxin, the target molecule caused to the formation of digoxin-aptamer complex and decrease of fluorescence intensity. The quenching of florescent had linear relation with digoxin concentration with detection limit of $29.87 \pm 1.01 \times 10^{-12}$ mol/L. Also, they used amine groups labeled aptamer in order to enhance the sensitivity and reproducibility of biosensor. By a two-step procedure, digoxin was determined more precisely. The fluorescence intensity of aptamer functionalized rGQDs firstly was turned-off utilizing oxidized CNTs (carbon nanotubes) via FRET (fluorescence resonance energy transfer) mechanism. Addition of digoxin and interacting with aptamer was resulted in the inhibition of CNTs connection with rGQDs-aptamer, so, the fluorescence of reduced GQDs was turned-on. The second procedure supplied a fast, low-cost, simple, ultrasensitive and reproducible method for detection of digoxin with ultra-low limit of detection, $7.95 \pm 0.22 \times 10^{-12}$ mol/L. Both of the developed luminescent apta-nano-biosensors were applied for qualification of target molecule in urine and human serum with acceptable analytical results [59].

3.3. Warfarin

Warfarin (WAR, 3-(α-acetonylbenzyl)-4-hydroxycoumarin) is broadly utilized as a blood anticoagulant in a variety of cerebrovascular and cardiovascular disorders like atrial fibrillation, pulmonary embolism, venous thromboembolism, coronary heart diseases and valvular heart disease for preventing and treatment of diseases [60–62]. Warfarin has narrow therapeutic index and required careful controlling of the patients. The dosage of oral anticoagulants has to be adjusted precisely and repeatedly for warranting the safety and effectiveness of them. If the administered dosage of warfarin exceeds the therapeutic window, it will results in the undesired bleedings [63]. Warfarin with an enolic group is

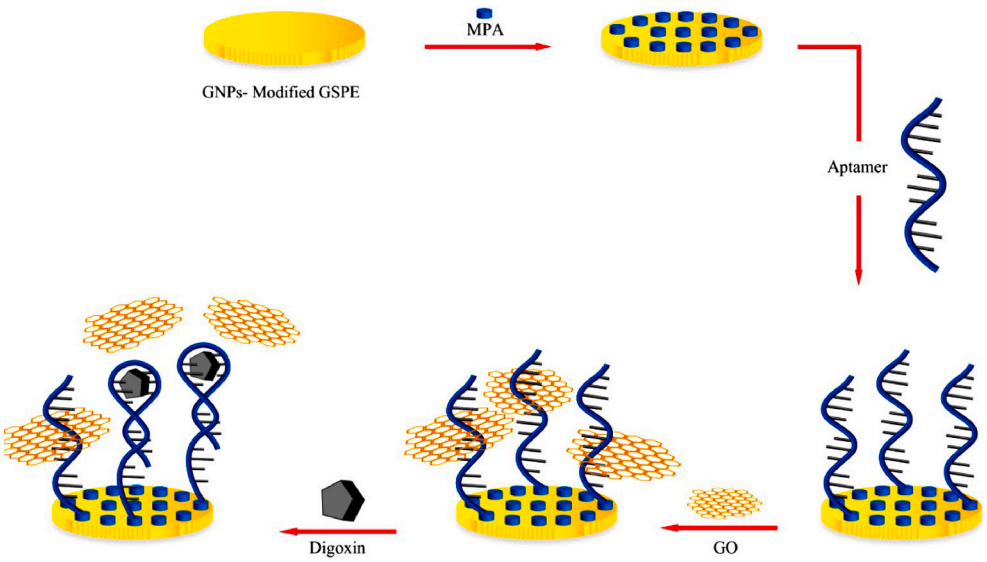


Fig. 1. *A schematic illustrating application of AuNPs in modification GSPE for detection of digoxin employing GO signal-on strategy* [58].

a less acidic drug and known as inhibitor for spread of tumor as well as stimulator of macrophages, lymphocytes, and granulocytes [64,65]. WAR therapeutic concentration is around 2.0–5.0 μg/ml with prolonged half-life which is 20–60 h (approximately 40 h) [66]. The usual side effects of WAR are including nausea, bleeding, stomach pain, vomiting, gas, bloating and the most serious and significant adverse reaction is hemorrhage which is life-threating also can lead to death. Hence, determination of WAR in clinical and biological samples is very prominent [60–62]. To date, a number of different techniques have been employed for determination of warfarin such as CZE (capillary zone electrophoresis) [67], MEKC-ESI-MS (micellar electrokinetic chromatography electrospray ionization mass spectrometry) [68], HPLC with fluorescence or UV determination [63,69,70], LC-MS/MS [71], and SFCMS/MS (supercritical fluid chromatography – tandem mass

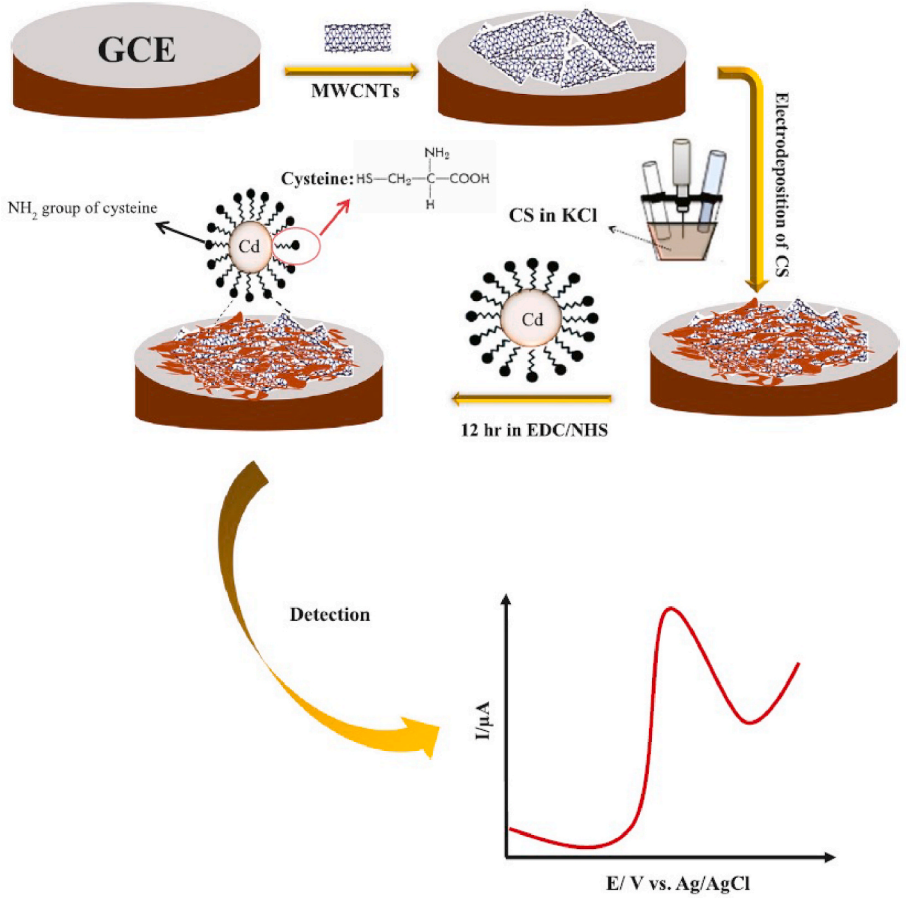


Fig. 2. *A schema representing the stepwise construction process of CdS-QD/MWCNT/CS modified GCE* [74].

spectrometry) [72]. However, these techniques suffer from serious and severe problems including being high-cost instruments, tedious and time consuming, great toxicity, large volumes of biological fluids and toxic solvents. For this purpose, electrochemical biosensors have drawn lots of interest for detection of warfarin due to their high sensitivity and selectivity, low-cost, simplicity and fast operation [73–75].

A new biosensor for warfarin detection based on modification of carbon paste electrode (CPE) with MWCNTs and $ZnCrFeO_4$. CV, DPV, chronoamperometry and EIS was applied to evaluate the behavior of modified electrode. The obtained results demonstrated that MWCNTs/$ZnCrFeO_4$ modified electrode had excellent electocatalytic effect for oxidation of warfarin. The linear concentration range for warfarin detection was 0.02–920.0 μmol/L with 0.003 μmol/L detection limit [76]. In order to detect warfarin, a CPE was chemically modified with $MnFe_2O_4$ incorporated into MWCNTs. MWCNT/$MnFe_2O_4$ modified electrode exhibited great electrocatalytic activity for oxidation of WAR and generating sharp peak current. The liner range for warfarin was between 0.10 and 447.0 μmol/L with 0.08 μmol/L LOD. The applied biosensor was greatly selective, fast, accurate and simple for detection of WAR in biological fluids [77]. In a study, an electrochemical biosensor was designed for detection of warfarin based on immobilization of CdS-QDs (CdS-quantum dots) onto carboxylated MWCNTs/CS (chitosan) compound film on the GCE surface (Fig. 2). The electrochemical behavior of CdS-QDs/MWCNTs/CS modified GCE was investigated by CV, DPSV (differential pulse stripping voltammetry) and EIS. The biosensor demonstrated anodic striping response within 90 s at 0.75 V accumulation potential. The modified GCE was employed for determination of WAR in 0.05–80 μM linear range and 8.5 nM limit of detection. The developed biosensor showed reproducibility, repeatability, and excellent stability as well as successful application for warfarin determination in serum, urine and milk samples [74].

Another sensitive biosensor was designed for WAR detection based on the molecular imprinting technique through electrodeposition of o-PD (*o*-phenylenediamine) and f-MWCNTs (possessing carboxylic functional group) on the surface of GCE. Thin film of MIP (molecularly imprinted polymer), which had binding sites special for warfarin, was electrochemically deposited on the surface of modified GCE. The last modification of electrode was applying AuNPs on the molecularly imprinted polymer surface (AuNPs/MIP/f-MWCNTs/GCE) (Fig. 3). The prepared AuNPs/MIP/f-MWCNTs modified GCE showed great selectivity and rapid binding kinetics because of their high affinity, large surface/volume ratios and great surface imprinted sites ratio. The linear warfarin concentration range was from 0.031 to 0.616 ng/ml and limit of detection was 0.024 ng/ml. The designed biosensor was detected WAR in human serum specimen [75].

By electrodeposition of cobalt oxide nanoparticles on MWCNTs modified GCE, another type of biosensor was prepared for the determination of warfarin. Application of cobalt oxide nanoparticles in fabrication steps of biosensor resulted in accumulation of warfarin and enhancement of electrochemical response. Under optimum conditions, DPASV (differential pulse adsorptive anodic stripping voltammetric) response of prepared electrode showed 3.3 nM LOD, 8 nM-50 μM and 50 μM–800 μM linear ranges. The fabricated biosensor was successfully applied in plasma and urine samples for WAR determination [78]. Gholivand and colleague designed a fast, highly selective and sensitive technique for simultaneous detection of mycophenolic acid (MPA) and warfarin through application of β-cyclodextrin (β-CD)/MWCNTs/cobalt oxide nanoparticles (Co3O4NPs) modified carbon paste electrode (CPE). CV and DPV were applied for evaluating electrochemical response and EIS (electrochemical impedance spectroscopy) was employed for study the surface modification of electrode. Under optimum conditions, the concentration range was 0.5–200 μM and 0.05–150 μM for MPA and WAR, respectively. In addition, the detection limits for MPA and WAR were 0.03 and 0.02 μM. The designed biosensor was employed in human serum and urine samples for detection of MPA and WAR with reasonable results [79].

4.3. Theophylline

Theophylline (THEO) with the IUPAC name of (3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione), as a methyl xanthine derivative is the most abundant xanthine in nature [80]. Its main metabolite, caffeine (CAF, 1,3,7-trimethylxanthine), categorized as alkaloid, is found in drinks and foods such as cocoa beans, coffee, cookies, tea, beverage and chocolate, and is gaining attentions as with its advantages in antioxidant and anticancer [81,82]. Theophylline is one of the most commonly clinically consumed drugs in the world and broadly utilized as a respiratory stimulator and bronchodilator in the treatment of chronic bronchitis, asthma, and sometimes in cardiovascular diseases. The main therapeutic application of theophylline is to boost relaxation of bronchial smooth muscle in the clinical setting of chronic and acute bronchospasm. Also, it is employed as a cardiac and diuretic stimulant [83–85].

The therapeutic level of theophylline is 55–110 mM (10–20 mg L^{-1}), lower than this level are generally non-therapeutic whereas levels as high as 330 mM (60 mg L^{-1}) may lead to sever toxicity [86]. Theophylline has narrow therapeutic index. Hence, monitoring the serum level of theophylline is crucial in order to hinder toxicity. Higher doses can

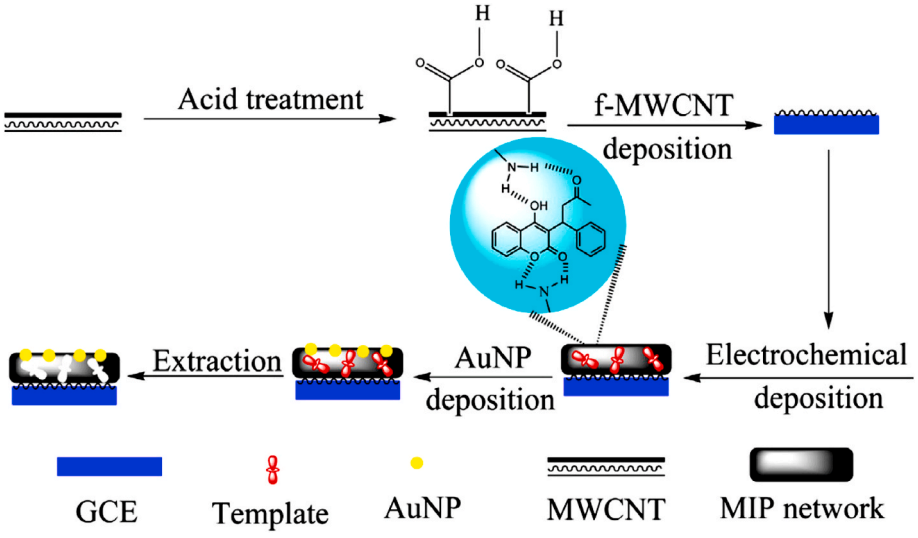


Fig. 3. *Schematic representation of fabrication steps of AuNPs/MIP/f-MWCNTs modified GCE for warfarin determination* [75].

lead to undesirable and distasteful side effects including tachycardia, anxiety, diarrhea, anorexia, dizziness, metabolic acidosis, insomnia, augmented heart rate, restlessness, hypokalemia, and even seizure [81, 87,88].

The detection of theophylline in various human fluids, like serum, urine, tissue and plasma is of intense interest in studies of human liver metabolism and experiments of clinical pharmacokinetic [89].

Consequently, determination of theophylline through reliable and uncomplicated method is highly preferable. Until now, much number of analytical techniques were used to detect the theophylline, for instance, gas chromatography-mass spectrometry [90], high Performance Liquid Chromatography [91], thin layer chromatography [92], capillary electrophoresis [93], fluorescence polarization [94] and immunoassay [95]. However, these techniques are time-consuming, expensive, inconvenient and laborious whereas the electrochemical techniques are very attractive because of their great sensitivity and stability, cheap and reasonable, fast in response, using equipment with ease. The challenging part in this technique of analysis is employing suitable modifiers for modifying the electrode in order to improve proficiency of electrochemical assay. Lately, thanks to nanotechnology and nanoscience, the construction of electrodes that chemically modified with nanomaterials have been vastly progressed [96,97].

In a recent study by Ganjali and colleagues, a new biosensor was designed in which the surface of SPE (screen-printed electrode) was modified with GQDs (graphene quantum dots) for determination of theophylline. The bare SPE was coated with GQDs through an uncomplicated method. Function of SPE modified with GQDs (GQD/SPE) was evaluated by CV (cyclic voltammetry) and revealed electroactivity enhancement in the theophylline oxidation in buffer phosphate solution. CV, DPV (differential-pulse voltammetry) and CHA (chronoamperometry) were employed to evaluate the sensitivity of GQDs modified SPE toward determination of theophylline. A broad linear range of concentration (1.0–700.0 μM) and LOD (limit of detection) of 0.2 μM was obtained under optimum conditions. The designed biosensor was successful in the evaluation of theophylline in real specimens [96]. Wang and co-workers fabricated a facile and novel electrochemical biosensor based on modification of GCE (glassy carbon electrode) with N-CNTs (nitrogen-doped carbon nanotubes) decorated with PLCY (poly (L-Cysteine)) for synchronous voltammetric detection of THEO (theophylline) and CAF (caffeine). The structure and morphology of multilayer film modified on the GCE surface were investigated by Raman Spectroscopy, SEM (Scanning Electron Microscope) and TEM (Transmission Electron Microscope). The characteristics of modified electrode were evaluated by CV, CC (chronocoulometry) and DPV, which were used to explore the electrochemical manner of theophylline and caffeine on the modified electrode. The results demonstrated that the detection towards CAF and THEO can be performed at the same potential range with respectively non-interfering and separated oxidation current peak. In comparison with bare electrode, the poly (L-Cysteine)/N-CNT/glassy carbon electrode can signally lead to improvement of electrocatalytic activity against the oxidation of CAF and THEO with a notable increment in anodic peak currents of 465.48% and 495.94%. Under the optimum circumstances, the fabricated composite film modified biosensor had great performance in detection of caffeine and theophylline with an expanded dynamic linear range from 0.40 to 140.0 μM and 0.10–70.0 μM, and detection limit of 0.20 μM and 0.033 μM, respectively. The poly (L-Cysteine)/N-CNT/GCE biosensor also possessed benefits like great sensitivity, reproducibility, stability and easy construction (Fig. 4) [41].

A new theophylline biosensor was fabricated utilizing a SWCNT (single walled carbon nanotube)-LMC (large mesoporous carbon)-Nafion compound modified GCE (SWCNT-LMC-Nafion-GCE). The morphology of single walled carbon nanotube-large mesoporous carbon was characterized by TEM (transmission electron microscopy) and the modified electrode surface was characterized by CV. The results demonstrated improvement of theophylline's voltammetric response and electrochemical reactivity. Under the selected circumstances the limit of detection was 0.08 mM with 0.3–38.0 mM linear concentration range as detected by DPV. The SWCNT-LMC-Nafion-GCE showed successful application for determination of theophylline in human urine and blood serum specimens with excellent recoveries [89]. An electrochemical detection of theophylline and norepinephrine was developed

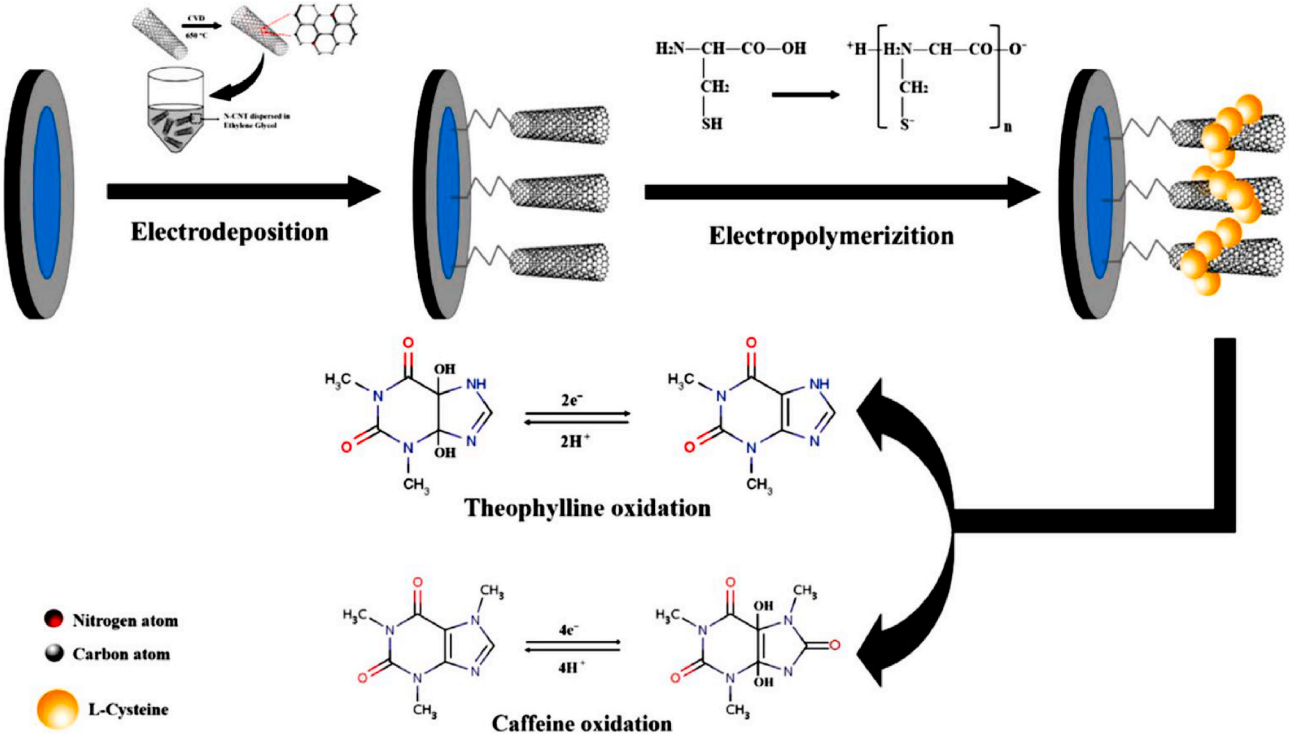


Fig. 4. *A schema representing the synthesis of poly (L-Cysteine)/N-CNT/glassy carbon electrode and CAF and THEO electrochemical oxidization* [41].

by utilizing ERGO (electrochemically reduced graphene oxide) modified GCE. Fabrication of ERGO on the surface of GCE was followed by self-assembling of GO (graphene oxide) on preassembled 1,6-HAD (hexadiamine) on the GCE through electrochemical reduction of graphene oxide. SEM imaging exhibited an aggregated formation for substrate modified with ERGO whereas a flake-like formation was observed for substrate modified with GO. Then, the GCE modified with ERGO was applied for determination of theophylline and norepinephrine. It was observed that the ERGO modified GCE not only improved the oxidation currents of theophylline and norepinephrine, but also led to prevention of effect of surface fouling which caused through oxidation products. In contrast, the theophylline and norepinephrine oxidation currents were low at graphene oxide modified GCE and bare electrode and significantly, because of the surface fouling effect their signals of oxidation were unstable. The GCE modified with ERGO leads to separation of oxidation signals of theophylline and norepinephrine in a compound and therefore utilized for their synchronous detection. By GCE modified with ERGO the selective detection of norepinephrine was achieved in the existence of higher concentrations of theophylline. Employing amperometry, a determination of 50 nM theophylline and 40 nM norepinephrine was obtained. By increment of theophylline and norepinephrine concentration from 5×10^{-8} - 4×10^{-5} M and 4×10^{-8} - 1×10^{-4} M, their current responses were boosted and LODs were 2.9×10^{-9} M and 8.4×10^{-10} M, respectively [98]. Treatment of HCAP (healthcare-associated Pneumonia) caused by MRSA (Methicillin-resistant *Staphylococcus aureus*) needs therapeutic procedures formed of LIN (linezolid) either in combination with THEO and MERO (meropenem) or alone. A sensitive SWV (square wave voltammetry) method was developed by using a carbon paste electrode modified with MWCNTs (multi-walled carbon nanotubes) in Britton-Robinson buffer. The sensor was applied at pH = 11.0 for detection of linezolid in plasma without interference within 2.5×10^{-8} - 8.0×10^{-6} mol L^{-1} concentration range. On the other hand, synchronous determination of LIN, THEO and MERO in plasma was possible at pH = 3.0 over 4.0×10^{-7}- 9.0×10^{-5}, 8.0×10^{-7} - 9.0×10^{-5} and 8.0×10^{-7}- 9.0×10^{-5} mol L^{-1} concentration ranges, respectively [99]. Further examples of THEO determination using carbon nanomaterials were described in Table 2.

Table 2
Analytical techniques for determination of THEO with modified electrodes.

Method	Modifier	Electrode	concentration range	limit of detection (LOD)	Ref.
SWV	MWCNTs/Au/poly-L-lysine	Screen printed	10 μM to 200 μM	2.0 μM	[100]
DPV	MWCNTs/MnO2 nanoparticles	Glassy carbon	0.1 μM to 20 μM	0.01 μM	[101]
DPV	GQD	Screen printed	1 μM to 700 μM	0.2 μM	[96]
DPV	GNP–CHIT–IL hybrid/r-GO	Glassy carbon	2.50×10^{-8}–2.10×10^{-6} mol L^{-1}	1.32×10^{-9} mol L^{-1}	[102]
DPV	MWCNT	Carbon paste	2.0×10^{-6} to 1.5×10^{-4} M	1.97×10^{-8} M	[103]
CV	MWCNT	Glassy carbon	3×10^{-7} to 1×10^{-5} mol L^{-1}	5×10^{-8} mol L^{-1}	[87]
DPV	MWCNT/ionic liquid (IL)	Glassy carbon	0.5 to 98.0 μM	0.16 μM	[104]
FFTCAV (FFT Coulometric Admittance Voltammetry)	AuNPs/MWCNT-Chitosan	Carbon paste electrode containg SiC NPs and IL	2 to 100 nM	0.39 nM	[105]
SWV	Graphene/ethyl 2-(4-ferrocenyl-[1,2,3] triazol-1-yl) acetate (EFTA)	Carbon paste	2.0×10^{-5} –1.0×10^{-3} M	1.56×10^{-5} M	[106]
SWV	P(LAsp)/f-MWCNTs/GCE	glassy carbon	0.1 to 50 μM	0.02 μM	[107]
DPV	poly(folic acid)/graphene composite film	Glassy carbon	0.2 to10 μM	0.03 μ mol L-1	[108]
DPV	MnO_2 nanosheets/IL-graphene	Glassy carbon	1 to 220 μM	0.1 μM	[109]
CV	Poly(Alizarin Violet 3B)/MWCNTs/ graphene	Glassy carbon disk	0.5 to 120 μM	0.02 μM	[110]
CV, SWV, CHA	1,4-BBFT/IL/GPE[1]	Carbon paste	1.2×10^{-5} -1.2×10^{-3} mol L^{-1}	9.2×10^{-6} mol L^{-1}	[111]
Fluorescent biosensor			0.1–10 μM		[112]
DPV	Aligned carbon nanotubes (ACNTs)	Glassy carbon	8.0×10^{-8}–1.0×10^{-5} M	1.6×10^{-8} M	[113]
LSV (linear sweep voltammetry)	ED-GO (electrodeposition GO)	Glassy carbon	8.0×10^{-7} to 6.0×10^{-5} mol L^{-1}	1.0×10^{-7} mol L^{-1}	[114]
DPV	AuNP/l-cysteine (l-cys)/Graphene/ Nafion composite film	Glassy carbon	4.0×10^{-9} to 6.0×10^{-5} mol L^{-1}	4.0×10^{-10} mol L^{-1}	[115]
DPV	Graphene-Nafion	Glassy carbon	1.0×10^{-8} – 1.0×10^{-6} and 2.0×10^{-6} – 3.0×10^{-5} mol L^{-1}	6.0×10^{-9} mol L^{-1}	[116]
DPV	Nafion/MWCNTs	Glassy carbon	8.0×10^{-8}–6.0×10^{-5} mol L^{-1}	2.0×10^{-8} mol L^{-1}	[117]
CV	MWCNTs/Pt_{nano}/[omim][PF_6][2]	Glassy carbon	1.0×10^{-8}–1.0×10^{-5} M	8.0×10^{-9} M	[118]
CV, DPV, EIS[3]	AuNP-MWCNT	Glassy carbon	0.5 to 20 μM	90 nM	[119]
CV	adenosine (AD)	Glassy carbon	3.0×10^{-8}-1.0×10^{-4} M	5.4×10^{-9} M	[120]
CV, DPV	WO3 nanoparticles[5]	Glassy carbon	2.5×10^{-8} – 2.6×10^{-6} M	8.3×10^{-9} M	[121]
CV, SWV	Graphene oxide/nanoclay (NC) composite	carbon paste electrode (CPE)	0.01 to 0.2 μM	1.80×10^{-9} M	[122]
CV	SA-MWCNTs[6] composite	Glassy carbon	0.01–60.0 μM	3.2 nM	[123]
CV, DPV	2eOHMnPc[7]-CNT	Glassy carbon	0.04–12 μM	0.0066 μM	[124]
FRET[4]	ssRNA aptamer/graphene oxide	——	10 to 300 nM	4 nM	[125]
Fluorometric	graphene oxide	——	0 to 1.0 μM	47nM	[126]

[1] 1-(4-bromobenzyl)-4-ferrocenyl-1H-[1,2,3]- triazole (1,4-BBFT)/ionic liquid modified graphene nano-sheets paste electrode
[2] Platinum nanoparticles (Pt_{nano}) decorated MWCNTs–1-octyl-3-methylimidazolium hexafluorophosphate ([omim][PF_6])
[3] Electrochemical impedance spectroscopy
[4] Fluorescence resonance energy transfer
[5] Tungsten trioxide nanoparticles
[6] Sodium alginate/multiwalled carbon nanotubes
[7] Manganese(III) phthalocyanine

4.4. Carbamazepine

Carbamazepine (CBZ), chemically termed 5-H-dibenz [b, f] azepine-5-carboxamide, is an imino-stilbene derivative of tricyclic compound which is greatly lipophilic. Carbamazepine has been utilized for more than three decades almost as a first choice in some of neurological and psychological disorders, in terms of mood stabilizing, anticonvulsive and antiepileptic drug for the treatment of bipolar disorder, epilepsy, trigeminal neuralgia, mental depression, and also for both partial and generalized seizure disorders thanks to the low incidence of chronic and acute toxicity and fast monitoring of extreme cerebral electrical discharges [7,127]. CBZ can also be employed to treat other illnesses such as neuromyotonia, schizophrenia, post-traumatic stress disorder (PTSD), ADHD (attention-deficit hyperactivity disorder), restless leg syndrome and ethanol withdrawal [128]. It has also superior efficacy in comparison to other antiepileptic drugs including phenobarbital, vigabatrin, valproate, primidone and gabapentin because of different action mode. Sometimes, it can also be utilized in non-epileptic therapy and can serves role as an agent for stabilization of mood [129].

Although, carbamazepine can lead to the production of some side effects like neurotoxicity, which results in dizziness, leukopenia, blurred vision, hypersensitivity and impaired task performance. Cases of nausea and vertigo stem from pharmacodynamic interaction of lamotrigine and carbamazepine also have been reported. The neurotoxicity of carbamazepine is extremely depends on the dosage and approximately 28% of orally administered CBZ is released via feces to the environment [130–133]. Oral dosage for daily administration of carbamazepine is varying from 200 mg to 1200 mg or more, which lead to an increment of plasma level of the drug (4–12 mg L^{-1}) [134]. CBZ because of being a broadly prescribed drug, recently is believed as a pollutant in surface and ground waters; hence, its accurate and fast determination by reliable techniques is much in demand [135,136]. Various analytical techniques have been employed for carbamazepine determination in biological samples and pharmaceutical formulations involving liquid chromatography [137,138], capillary electrophoresis [139], as well as electrochemical strategies [135,140]. Liquid chromatography was a recommended method for CBZ determination due to its selectivity and sensitivity, whereas it takes long time, needs costly maintenance and devices, and uses lots of solvent [141].

An amperometric biosensor was developed for carbamazepine detection based on the application of ERGO (electrochemically reduced graphene oxide) and SWCNT (single walled carbon nanotube) composite film on the surface of GCE. The π–π stacking interactions between SWCNT and ERGO were resulted in greater stability of composite. Comparison of GCE modified with SWCNT with the one modified with SWCNT-ERGO composite film was demonstrated an increment about 3.2 fold in carbamazepine oxidation peak current. The developed biosensor was detected carbamazepine within 50 nM to 3 μM linear range, 5.1076 μA μM^{-1} cm^{-2} sensitivity and detection limit of 29 nM [142]. In a recent study, a nanocomposite containing cerium (Ce) doped zinc oxide (ZnO) and reduced graphene oxide (rGO) (Ce–ZnO/rGO), which was prepared through low hydrothermal technique, was used for modification of GCE in order to detect CBZ. By CV (cyclic voltammetry), DPV (differential pulse voltammetry) and EIS (electrochemical impedance spectroscopy) the electrochemical characteristics were evaluated. The modified GCE showed a fast and great electro-oxidation response towards carbamazepine determination. Under optimum conditions, the linear concentration range for detection of CBZ was between 0.05 and 100 μM with 1.2 nM limit of detection as well as 0.086 μA nM^{-1} cm^{-2} sensitivity. In addition, the proposed method was exhibited prolonged stability, excellent reproducibility and enhanced selectivity. The developed biosensor was appropriate for detection of CBZ in real samples such as urine specimen and pharmaceutical tablets (Fig. 5) [143].

In a study, for determination of CBZ, a new Gr (graphene)-AuNPs (gold nanoparticles) composite was deposited on Au (gold) electrode in which the size of AuNPs was between 10 and 20 nm. CV, EIS and LSV (linear sweep voltammetry) were applied for evaluation of CBZ oxidation. The obtained results exhibited that the modified Au electrode had good electrocatalytic activity toward carbamazepine oxidation. In comparison to bare electrode, the peak current enhanced up to two times with shifting of peak potential to lower oxidation potential in modified electrode. The obtained limit of detection with Gr-AuNPs modified gold electrode was 3.03×10^{-6} M [144].

Currently, an electrochemical biosensor was designed for detection of CBZ and DA (dopamine) based on synthesis of Cu^{2+} loaded NaA (zeolite A) hybridized with NGr (nitrogen doped graphene) and its application for modifying GCE. The SWV (square wave voltammetry) was employed for evaluation of biosensor. The linear concentration ranges for CBZ and DA were 10–80000 nM and 4–100 nM, respectively. According to the obtained results the 3.8 and 6.3 nM LOD (limit of detection) was obtained for DA and CBZ, respectively [145]. Veiga and co-workers employed a GCE coated with MWCNTs film for voltammetric detection of CBZ. The modified electrode showed good electrocatalytic effect towards the carbamazepine oxidation. The voltammetric response

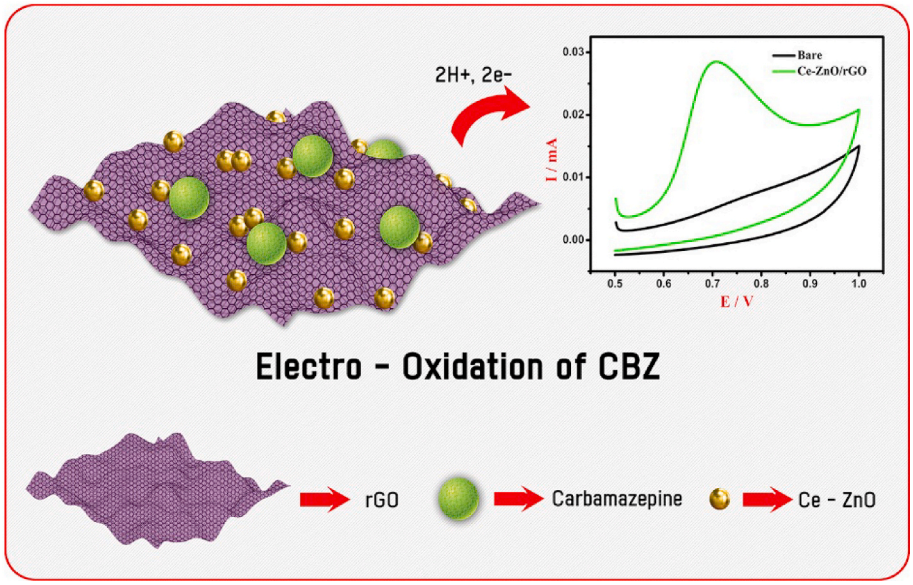


Fig. 5. A schema illustrating Ce–ZnO/rGO based biosensor for determination of carbamazepine [143].

for determination of carbamazepine with MWCNTs film modified electrode was enhanced significantly compared to the bare GCE. The results showed 0.13–1.60 μM linear range with 40 nM LOD and 140 nM LOQ (limit of quantification) which were the lowest amount among the reported methods. The suggested technique was employed for quantifying carbamazepine in pharmaceutical structures and wastewater specimens [146]. In another study, an electrochemical biosensor based on modification of GCE with fullerene-C_{60} was used for the determination of carbamazepine. CV results exhibited both reduction and oxidation peaks at fullerene-C_{60} modified GCE. The film on the surface of electrode showed great improvements on CBZ electrochemical response. The obtained linear range was from 90 nM to 10 μM with 16.2 nM LOD and 54.0 nM LOQ. The developed method was successfully employed for detection of carbamazepine in urine and spiked serum samples as well as pharmaceutical structures [147]. Daneshvar and colleagues fabricated a CILPE (carbon ionic liquid paste electrode) based on trifluoromethylsulfonyl (butyl-3-methylimidazolium bis) imide ([bmim] NTF2) which was then modified with Gr/MWCNT hybrid composite. The Gr/MWCNT/CILP modified electrode was employed for the determination of CBZ in the existence of PA (paracetamol) with a great electrochemical catalytic feature. The modified electrode application was evaluated by CV and DPV. The linear ranges for detection of PA and CBZ were 2–80 μM and 1–60 μM, respectively. Furthermore, the limits of detection for PA and CBZ were 0.262 μM and 0.233 μM, respectively. The designed biosensor was successfully used for carbamazepine and paracetamol detection in urine specimens and tablet [148].

4.5. Phenobarbital

Phenobarbital (phenobarbitone, 5-ethyl-5-phenylbarbituric acid; PB) is the most prevalent and eldest anticonvulsant and still is the most broadly prescribed drug for epilepsyall over the world [149,150]. Phenobarbital is efficient in severe brain disorder, clonic-tonic crisis and also has some sedative and relaxing effects. If phenobarbital uses for long time it will cause tolerance effects [151]. Various analytical techniques have been used for PB determination in biological samples or pharmaceutical formulations such as liquid chromatography [152], potentiometric method [153], and capillary electrophoresis [154]. However, these techniques have high-cost, are time-consuming, and uses high solvents. Recently, biosensors have showed a broad spectrum of economic and simple analysis.

An electrochemical biosensor was prepared based on MWCNTs and Pt nanoparticles for determination of PB in the existence of AC (acetaminophen). The modified electrode demonstrated good behavior for electrocatalytic oxidation of AC and PB. DPV peak currents of PB and AC enhanced linearity within 0.4–60 μM and 0.5–100 μM linear ranges, respectively. The limit of detection for PB and AC were 0.1 μM and 0.17 μM, respectively. The proposed method was successfully used for phenobarbital and acetaminophen detection in pharmaceutical and urine samples and had good stability and reproducibility [155]. Another biosensor was designed based on rGO (reduced graphene oxide)/Pt nanoparticles composite which was immobilized on GCE surface. The modified electrode demonstrated good electrocatalytic activity toward PB and DDP (droxidopa). The electrochemical behavior of biosensor was investigated by CV, DPV and the obtained oxidation peak for PB and DDP was around 230 mV. The obtained limits of detection for PB and DDP were 2.36×10^{-8} M and 3.1×10^{-8} M, respectively [156]. Shariati and co-workers designed sensitive and selective fluorescence biosensor based on application of MIPs (molecularly imprinted polymers) coated on the GSCDs surface (green source carbon dots) for determination of antiepileptic drugs and phenobarbital. In order to synthesize GSCDs via hydrothermal strategy, Cedrus employed as a source of carbon. The fluorescence probe, MIPs-GSCDs obtained through utilizing reverse micro-emulsion technique in order to coat thin film of silica on the GSCDs surface. Then, TEOS (tetraethoxysilane), APTES (3-aminopropyltriethoxysilane), and phenobarbital were used as cross linker, a functional monomer, and a template, respectively. The phenobarbital rebinding with molecularly imprinted polymers cavities led to selective quench of fluorescence signal of molecularly imprinted polymers/GSCDs. Under the optimal conditions, the linear range was 0.4–34.5 nmol/L with 0.1 nmol/L limit of detection. The potential of biosensor in real specimen analysis examined through determination of phenobarbital in human blood plasma specimens [157].

4.6. Levothyroxine (T4)

Levothyroxine (T4) is a hormone produced by the thyroid gland. It is a derivative of thyronine and participates in regulating some important functions of the body from regulating metabolic activities and synthesis of carbohydrate and proteins to promoting developmental stages (neurons, reproductive organs, etc.). As the hormone has a narrow therapeutic index and is administered in very low doses (μg), it is clinically very important to warrant the drug efficient uptake [158–160]. Measuring T4 level may be performed using various procedures including chemiluminescence [161], capillary electrophoresis [162], gas chromatography mass spectroscopy [163], high performance liquid chromatography (HPLC) [164,165], immunoassay methods [166], and electrochemical methods [160,167]. However, most common methods include HPLC and immunoassay. On the other hand, most methods that work based on non-electrochemical features, although deliver precise measurements, need relatively long time, as well as sophisticated instruments and sample preparations to be completed. Electroanalytical assays also offer simple, sensitive, accurate, fast, and affordable methods to detect and determine pharmaceutic agents [168]. In a new study, Lofti and Veisi were able to effectively detect T4 (the range of 10–120 nM and a low detection limit of 2.84 nM) employing gold nanoparticles empowered on modified multi-walled carbon nanotubes and mercaptoethanol-bound melamine (MWCNTs/CC-S [169]H/AuNPs) on a glassy carbon electrode. The method developed by Lotfi et al. delivered acceptable detecting parameters (i.e. sensitivity, specificity, linearity, and reproducibility), and the detection capability of the modified electrode to measure T4 in pharmaceutical products (e.g. tablets) and human serum has been successfully validated by HPLC [169].

5. Conclusion

Precious monitoring of pharmaceuticals with narrow therapeutic index (NTI) is an important issue in the clinic, in order to avoid life threatening adverse reactions but also ensuring the sufficient effective dosage. Different studies have been done to introduce new biosensors for fast and reliable detection of NTI drugs and it seems that incorporation of carbon nanomaterials to the biosensor can be very effective. In this review, the notable literature of various carbon nanomaterial-based biosensors was discussed for the determination of NTI pharmaceuticals such as Carbamazepine, Digoxin, Phenobarbital, Warfarin, Theophylline and Levothyroxine (T4). These kinds of nanobiosensors are commonly applied because of their low-cost, excellent stability, biocompatibility, and good kinetics of electron transferring. Great efforts have been done in this field, and it might be possible in the near future the routine analytical instruments will be replaced by the reported nanobiosensors, which provided fast, simple, sensitive and selective detection of NTI drugs in biological and pharmaceutical samples.

Declaration of competing interest

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.

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Appendix A. Supplementary data

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