Electrochemical determination of paracetamol, rutin and sulfonamide in pharmaceutical formulations by using glassy carbon electrode – A Review

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Abstract: Recent advances in the electrochemical application of glassy carbon electrode for determination of selected drugs in pharmaceutical formulations are reviewed. Several analytical techniques such as liquid chromatography, high performance liquid chromatography, spectrophotometry, chemiluminescence, and capillary electrophoresis-mass spectrometry have been used for the detection and separation of pharmaceutical active components due to their high sensitivity and great selectivity. However, all these methods are complicated, time-consuming and require expensive equipment. In contrast to these conventional techniques, the electrochemical technique overcomes those drawbacks owing to its low cost, rapid response and application in on-site test. Special attention is paid on this review for electrochemical application of bare and modified glassy carbon electrode for the determination of paracetamol, rutin and sulfonamide.

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PUBLIC INTEREST STATEMENT

Various analytical methods have been reported to examine the therapeutic efficacy of drug in pharmaceutical formulation and biological samples. However, most of these methods are complicated and expensive equipment. Electrochemical methods, on the contrary, are simple, selective, and environmentally friendly making them of choice for the determination of drugs.

The active ingredient in paracetamol, rutin and sulfonamide are electroactive that can be detected using voltammetric techniques. Glassy carbon (GC) is widely used electrode materials reported for the analysis of the aforementioned drugs which might be due to its wide potential range, greater inertness to chemical attack, excellent mechanical and electrical properties. Modification of an electrode surface including GCE usually improves its response for the analyte may be due to increased surface area, adsorption, or electron exchange.

This review thus demonstrates the application of modified glassy carbon electrodes for the determination of the three selected drugs and shows the effect of the nature of the modifier on the performance of glassy carbon electrode towards an analyte.
determination of paracetamol, rutin and sulfonamide in pharmaceutical formulation.

Subjects: Analytical Chemistry; Medicinal & Pharmaceutical Chemistry; Physical Chemistry; Inorganic Chemistry

Keywords: electrochemistry; glassy carbon electrodes; pharmaceutical formulation; electrochemical methods

1. Introduction
The drug development process starts with the foundation of a drug molecule that has shown therapeutic value to battle, control, and check or cure diseases. The synthesis and characterization of such molecules which are also called active pharmaceutical ingredients (APIs) and their analysis was done for a long time by different analytical methods to examine their safety use and therapeutic efficacy of drug (Masoom et al., 2017; Nineza, 2010).

In pharmaceutics, the instrumental methods used for quantization of the drugs are most commonly divided into four basic categories: chromatographic, spectrophotometric, electrochemical, and radiometric analysis (Nineza, 2010).

From this liquid chromatography, high-performance liquid chromatography, spectrophotometry, chemiluminescence, and capillary electrophoresis-mass spectrometry are the conventional methods reported for the determination of pharmaceutical active components due to their high sensitivity and great selectivity (De-Abreu et al., 2003; Deng et al., 2008; Ge et al., 2013; Laina & Girish, 2013; Qader & Fakhre, 2017). However, all these methods are complicated, long analysis time, require expensive equipment, and the requirement for sample pretreatment when some procedures as derivatization, extraction and purification are usually included. In some cases, low sensitivity and selectivity can make these methods unsuitable for routine analysis. On the contrary electrochemical methods overcome those drawbacks owing to its low cost, rapid response and application in the on-site test (Hassaninejad & Shajie, 2017; He & Yan, 2017).

Thus, the development of a simple, cost-effective, and sensitive method is needed for the determination of electroactive ingredients in pharmaceutical formulations (Nikodimos & Amare, 2016). Therefore, electrochemical methods are chosen for the sensitive analysis of pharmaceutically active compounds in their dosage forms and biological samples, and also, important decisions are taken which are based on data obtained from real samples about drug resistance (Elyasi et al., 2013; Ensafi & Karimi-Maleh, 2010).

Electroanalytical methods used to obtain information related to the amounts, properties, and environments of chemical species. Analytical research on a drug substance starts after synthesis, with the characterization of its physicochemical properties to ensure that all pharmacological testings are done with pure material and to establish specifications so that future production lots will yield a reproducible in vivo response. These specifications will include studies of the purity of the drug, identification and quantization of other products of synthesis (He & Yan, 2017; Krimi et al., 2016).

Electrochemistry is a relatively clean chemical system, easy to control and can be studied in aprotic and aqueous solutions which allows to evaluate the behavior of free radicals generated in biological systems which received tremendous attention (Elyasi et al., 2013; Ensafi & Karimi-Maleh, 2010; Nineza, 2010).

Thus, voltammetry is an extremely sensitive electrochemical technique for measuring trace amount of pharmaceutically active compounds either in dosage forms or in biological samples using glassy carbon electrode which detects pharmaceutical active components selectively. Since pharmaceutical products are biologically active chemicals with functional groups that can undergo
redox processes, their redox activity can be detected by the cyclic voltammetry (Filik et al., 2014; Krimi et al., 2016).

In this review, reported research works on electrochemical applications of unmodified/modified glassy carbon electrode for the determination of paracetamol, rutin and sulfonamide in the pharmaceutical formulation are considered. Many researchers have reported that the use of bare electrodes for the detection of organic compounds presents a number of limitations (Krimi et al., 2016; Nineza, 2010). The use of modified electrodes has been proposed, where a variety of compounds have been used as electron transfer mediators for oxidation or reduction of several target molecules.

Modified electrodes possess distinct advantages over conventional electrodes in numerous application areas including electrocatalysis and electrochemical sensors. Therefore, the improvement in analysis using a modification of bare electrodes had been the motivation for different researches. In some cases, the electrochemical responses obtained do not have well-defined peaks when bare glassy carbon electrodes are used. For this reason, the modification of the surface of bare electrodes is done in order to improve the electrochemical responses of these groups (Filik et al., 2014).

The objective of this review was thus to show the contribution of electrochemical analysis on electroactive ingredients in pharmaceutical formulation using glassy carbon electrode, and also to summarize the performance and advantages of a modified glassy carbon electrode.

1.1. Pharmaceutical formulations
Pharmaceutical formulation, in pharmaceutics, is the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product. In addition to this formulation is often used in a way that includes dosage form (Rasool, 2012; Verma et al., 2013).

Formulation studies involve developing a preparation of the drug which is both stable and acceptable to the patient. It is important to make the distinction that a tablet contains a variety of other potentially inert substances apart from the drug itself, and studies have to be carried out to ensure that the encapsulated drug is compatible with these other substances in a way that does not cause harm, whether direct or indirect (Gad, 2008). Preformulation involves the characterization of a drug’s physical, chemical, and mechanical properties in order to choose what other ingredients (excipients) should be used in the preparation.

Formulation studies consider different factors as particle size, polymorphism, pH, and solubility, as all of these can influence bioavailability and hence the activity of a drug (Thapliyal et al., 2016). The drug must be combined with inactive ingredients by a method that ensures that the quantity of drug present is consistent in each dosage unit. The dosage should have a uniform appearance, with an acceptable taste, tablet hardness, or capsule disintegration.

In the case of formulation, consideration has to be given to what is known as “drug loading”—the ratio of the active drug to the total contents of the dose. A low drug load may cause homogeneity problems. A high drug load may pose flow problems or require large capsules if the compound has a low bulk density (Gad, 2008).

2. Methodology

2.1. Methods of modifying glassy carbon electrodes
All the important analytical properties of electrodes, namely, sensitivity, selectivity, reproducibility and even applicability, have been shown to be capable of enhancement by the wise use of modification. Electrochemical-based techniques using modified electrodes can be considered for
the determination of environmental, biological and pharmaceutical compounds as strong alternatives to the other instrumental methods (Ensafi & Karimi-Maleh, 2010; Ensafi et al., 2011; Karimi-maleh et al., 2013).

The chemically modified electrodes (CMEs) are very interesting and powerful tools for the analysis of many substances at trace level, by improving electrode sensitivity allowing detection of a wide range of electroactive compounds up to a very low detection limit (Fernandez & Carrero, 2005). A significant point in CMEs utilization in speciation work is to choose the most convenient modifier for each analyte because the sensitivity and selectivity of the electroanalytical response depend on the characteristics of the modifier (Krimi et al., 2016).

Electrode surfaces need to be protected against non-electroactive interferents, which can be irreversibly adsorbed on the surface of the electrode during voltammetric scans. These interferents lead to a decrease in electrode response with time and preclude the possibility of analysis of untreated samples. Such protection can be achieved by using suitable electrode materials or, alternatively, suitably modified electrode materials. Much attention has been devoted to carbon electrodes and their modification, given their widespread use in electroanalytical chemistry (Nineza, 2010).

The surface modification changes the surface layers of the electrode itself or creates a layer with some form of chemical as well as physical selectivity.

Modified electrodes can be prepared in the following ways.

(a) Chemical modification: The electrode surface is activated by chemical reaction, such as with silane, which is then used to react with another chemical species that becomes immobilized on the surface (He & Yan, 2017; Nineza, 2010).

(b) Adsorption: This is used for coating electrode surfaces with solutions of the modifier either by dipping or, more commonly, by applying a drop of the solution followed by spinning to evaporate the solvent (spin coating). This is particularly used for modifying with soluble polymers. Some polymeric species which have a tendency for self-assembly can also be applied through such procedures, leading to self-assembled monolayers on the electrode surface (Nineza, 2010).

(c) Electroadsorption and electrodeposition: The deposition of the substance on an electrode by the action of electricity (especially by electrolysis). If adsorption is carried out under the influence of an applied potential then thicker modifier layers usually result, but there is probably a greater guarantee of uniformity. Such procedures are used for the formation of conducting polymers (Nineza, 2010; Laina & Girish, 2013).

(d) Plasma: The electrode surface is cleaned by plasma leaving the surface with dangling bonds and being highly active. Adsorption of any species, such as amines or ethenes, in the vicinity, is very fast (Laina & Girish, 2013).

(e) Electropolymerization: used for the modification of electrode surfaces that can accelerate the transmission of electrons onto the surface of the electrode, it has high selectivity and sensitivity due to the film homogeneity in electrochemical deposition, and it has a strong adherence to the electron surface and large surface area (Ensafi & Karimi-Maleh, 2010).

Chemically modified electrodes comprise a relatively modern approach to electrode systems. They find utility in a wide spectrum of basic electrochemical investigations, including the relationship of heterogeneous electron transfer and chemical reactivity to electrode surface chemistry, electrostatic phenomena at electrode surfaces, and electron and ionic transport phenomena in polymers. The use of the chemically modified electrodes greatly improves the efficiency of accumulating target analytes without interferences compared with the conventional voltammetric techniques (Basgel & Erdemoglu, 2006).
Electrodes have been modified using electroactive polymers and polymeric composites, metal complexes, alloys, and quantum dots among others. Biomolecules such as enzymes, oligonucleotides, antigen/antibodies, and tissues as well as whole cells have been bioconjugated into chemically modified electrodes for biosensor fabrication.

The development of new materials for electrode modification that grossly alters the redox potentials to near-zero values (Laina & Girish, 2013), while at the same time distinguishing the redox potentials of target analytes that exhibit similar electrochemical properties in a complex matrix, ensuring high selectivity and sensitivity.

In recent years, the modification of electrode surfaces has been an important research area in electrochemistry. The species which are confined to the electrode surface provide an opportunity to study the basis of the electrochemical reaction. In electrochemistry, it has been demonstrated that modified electrodes possess distinct advantages over conventional electrodes in numerous application areas including electrocatalysis and electrochemical sensors (Garazhian & Shishehbore, 2015). Modified electrodes are able to catalyze the oxidation and reduction of solute species which exhibit high overpotential at unmodified electrode surfaces. They offer a possibility of lowering the overpotential and increasing sensitivity and selectivity of some electroactive species (Ninez, 2010).

2.2. Measurement procedures

For characterizing the electrochemical behavior of the electroactive ingredient in pharmaceutical formulation at the unmodified and modified electrode, voltammetric methods used a three-electrode configuration with glassy carbon electrode as working electrode and Pt wire and saturated Ag/AgCl as counter and reference electrodes, respectively (Filik et al., 2014; Hassaninejad & Shajie, 2017).

The working electrode (either bare/modified glassy carbon electrode) was placed in appropriate buffer solutions, with suitable pH when the peak current is maximum, containing desired concentrations of pharmaceutical samples before starting the scan (Ge et al., 2013). CV, DPV and SWV techniques were used for the determination of pharmaceutical samples and all electroanalytical measurements were made at room temperature (Filik et al., 2014). The performed initial and final potential were variable, depending on the pH value and the cut-off of the electrolyte (Huang et al., 2014).

3. Review on the application of glassy carbon electrode for determination of paracetamol, rutin and sulfonamide in pharmaceutical formulations

Electrochemistry is a well established and fast-growing area with a number of possible applications in the pharmaceutical field. Electrochemical methods are habitually used in analytical chemistry. The improvement of quality of life has stimulated considerable research in drug design bioavailability and safety. Voltammetry is an extremely sensitive electrochemical technique for measuring trace amount of pharmaceutically active compounds either in dosage forms or in biological samples. In drug analysis, voltammetric techniques are very popular because of the low quantification limit, its accuracy and precision, as well as the low cost of equipment compared to other analytical methods (Elyasi et al., 2013; He & Yan, 2017).

In this review, only selected research investigations that involved on the electrochemical application of glassy carbon electrode for the analysis of electroactive ingredients on pharmaceutical formulation were considered.

3.1. Electrochemical nature of Paracetamol

Paracetamol (Acetaminophen: N-acetyl-p-aminophenol) is one of the most commonly used analgesics in pharmaceutical formulations, for the reduction of fever and also as a painkiller for the relief of mild to moderate pain associated with headache, backache, arthritis and postoperative pain (Amare, 2019; Filik et al., 2014).
A variety of techniques including high-performance liquid chromatography (Baranowska & Kowalski, 2010; Hadad et al., 2009), and liquid chromatography-mass spectroscopy (Lohmann & Karst, 2006; Lou et al., 2010) have been reported for the determination of paracetamol in various types of samples.

The electrochemical behavior of paracetamol (PCT) both at unmodified glassy carbon electrode and Fe(III) doped zeolite-graphite composite modified GC electrode (FZ-G/GCE) has been investigated using cyclic voltammetry (Amare, 2019). As presented in Fig.1, while the unmodified GCE showed a poor electrochemical response for paracetamol, the Fe(III) doped zeolite-graphite composite modified GCE showed an enhanced electrochemical signal for paracetamol of the same concentration (Amare, 2019).

At the bare GCE (figure 1A, curve b), a pair of relatively weak oxidative and reductive peaks with peak-to-peak potential separation ($\Delta E_{p} = E_{pa} - E_{pc}$) of 273 mV.

In contrast to the bare GCE, the Fe(III) doped zeolite-graphite composite modified GCE showed a pair of well-defined redox waves with a reduced peak-to-peak potential separation ($\Delta E_{p}$) of 142 mV and an enhanced peak current values (curve b of figure 1B). Lower peak potential separation and enhanced peak current of the PCT at the modified GCE than at the unmodified GCE illustrated fast electron transfer and hence catalytic activity of the modifier towards the redox process of PCT (Amare, 2019).

Figure 2 presents the square wave voltammograms of various concentrations of PCT at Fe(III) doped zeolite-graphite composite modified GCE (Amare, 2019).

As can be seen from the figure, the peak current increased linearly with PCT concentration in the concentration range of 5.0$\times$10$^{-7}$ - 2.0$\times$10$^{-5}$ M with detection limit of 1.0$\times$10$^{-8}$ M (Amare, 2019) illustrating the applicability of the modified GCE for determination of paracetamol at low concentration.

The performance of FZ-G/GCE was comparison with other modifier reported in literature presented in Table 1. As can be observed from the table 1, the method using FZ-G/GCE showed the least detection limit and wide linear dynamic range making it applicable for determination of PCT at low concentration levels.

### 3.2. Electrochemical behavior of rutin

Rutin (3’,4’,5,7-tetrahydroxyflavone-3β-D-rutinoside) is one of the most abundant bioactive flavonoids called vitamin P known to act as scavenger of various oxidizing agents including superoxide anions, hydroxyl radicals, and peroxyl radicals (Gholivand et al., 2016; Chen et al., 2010).
As a result of this, its several pharmacological activities including antibacterial, anti-inflammatory, antitumor, antiallergic, antiviral and antiprotozoal properties have been widely used making its determination in real samples of considerable interest. Capillary electrophoresis, high performance liquid chromatography, spectrophotometry and electrochemical techniques have been used to determine rutin (Gholivand, et al., 2016; Chen et al., 2010).

Rutin being an electroactive compound, its electrochemical behavior has been studied by cyclic voltammetry using bare glassy carbon electrode (GCE), chitosan (CS) modified GCE, multiwall carbon nanotubes (MWCNT) modified GCE, CS/MWCNT modified GCE and Cu-CS/MWCNT film-
modified GCE. As presented in figure 3, rutin showed a pair of redox peaks whose peak current significantly increased from the unmodified to the Cu-CS/MWCNT modified GCE (curve a to e) (Gholivand, et al., 2016).

As For the CS/GCE enhance the anodic peak current of rutin without any significant change in its cathodic peak current. This enhancement may be due to rutin adsorption at the surface of the electrode (Figure 3, curve b). Furthermore, the peak-to-peak potential separation increased when the CS/GCE was used which may be due to less effective electron conductivity of the chitosan film, which was limited electron transfer process on the surface of the electrode, however, modifying the GCE with MWCNTs enhance the electrochemical signal of rutin both the anodic and the cathodic peak currents, and also enhanced the process reversibility by decreasing the peak potential separation (Figure 3, curve c). This indicates that the presence of MWCNTs can dramatically increase electron transfer to the electroactive molecules on the electrode surface. Further enhancements were observed in both peak currents when the combination of MWCNTs and chitosan was used as a modifier (Figure 3, curve d).

In contrast to the unmodified GCE, the Cu-CS/MWCNT/GCE showed well resolved oxidation and reduction peaks (curve e of Figure 3). The peak current of rutin at the Cu-CS/MWCNT-modified glassy carbon electrode was about 10 times larger than the current at the unmodified GCE. The increased peak current response at the polymer modified GCE was attributed to an increased adsorption of the modifier for rutin (Gholivand, et al., 2016).

This illustrated fast electron transfer and hence the catalytic activity of the modifier (Cu-CS/MWCNT/GCE) towards the redox process of rutin (Gholivand, et al., 2016).

Similarly, Figure 4 also presents the calibration curve for the differential pulse voltammetric determination of rutin using Cu-CS/MWCNT-modified GCE (Gholivand, et al., 2016). The current response of Cu-CS/MWCNT/GCE showed linear dependence on the concentration of rutin in the range of 5×10⁻⁸ - 1.0 ×10⁻⁴ M with the detection limit of 1 × 10⁻⁸ M. In addition, the relative standard deviation (RSD) of the eight times repeated determination of 1.0 × 10⁻⁶ M rutin was less
than 5.0% (Gholivand, et al., 2016), indicating that the modified electrode showed good reproducibility and can detect trace amount of the rutin. After the electrode was stored for 4 weeks, no apparent decrease of the electrochemical response to rutin was observed, which indicated the good stability of the modified electrode (Gholivand, et al., 2016).

As can be seen from the table 2, the Cu-CS/MWCNT/GCE showed relatively of wider linear dynamic range and of course reasonable limit of detection indicating its applicability for the determination of rutin in a wide range of its low concentration.

### 3.3. Electrochemical properties of sulfonamide

Electrochemical properties of Sulfonamide were investigated using glassy carbon electrode modified by Fe₃O₄/functionalized graphene (He & Yan, 2017).

Sulfonamide is a group of synthetic antibiotic drugs which is effectively employed in the prevention and treatment of infectious diseases caused by gram-positive, gram-negative bacteria and some protozoa. Due to low cost and wide antimicrobial spectrum, sulfonamide has been widely used as veterinary drugs in animal caring. But improper utilization will cause enrichment of sulfonamide in the animal body and result in side effect to the human body.
directly or indirectly. Consequently, it is essential to develop valid methods for the determination of sulfonamide quantitatively (He & Yan, 2017).

Several analytical techniques such as liquid chromatography, high-performance liquid chromatography, spectrophotometry, chemiluminescence, and capillary electrophoresis-mass spectrometry have been used for the detection of sulfonamides due to their high sensitivity and great selectivity.

The electrochemical performance of sulfonamide has been studied by cyclic voltammetry using bare glassy carbon (GC) electrodes and Fe₃O₄-functionalized graphene-modified GC electrodes (He & Yan, 2017).

As presented in Figure 5, unmodified GCE showed no response in the absence of sulfonamide (curve a Figure 5) whereas a weak anodic peak (curve b Figure 5) for the 0.1 mM sulfonamide. In contrast to the unmodified GCE, the response of the GCE for sulfonamide was improved by modifying its surface by functionalized graphene (Gr) (curve c Figure 5) which of course was further improved by modifying the surface of the GCE by a composite of Gr and Fe₃O₄ (curve d Figure 5)(He & Yan, 2017).

Table 3 presents the performance of the Gr/Fe₃O₄/GCE for determination of sulfonamide compared to previously reported electrodes. As can be observed from the results in the table, the Gr/Fe₃O₄/GCE exhibits a wider linear dynamic range where current response is varied linearly with concentration and lowest detection limit indicating Gr/Fe₃O₄/GCE was more suitable for the detection of sulfonamide.
4. Conclusions
There is clearly a growing demand for rapid, reliable, inexpensive carbon-based electrode materials for the measurement of the drug compounds. These electrodes proved to possess unique chemical and structural features that make them very attractive for electrochemical studies and electroanalytical applications. Carbon-based electrodes have been used successfully in proof-of-principle research studies to the pharmaceutical compounds in their dosage forms and in biological samples. Different types of carbon-based electrodes have emerged over the last few years, significantly changing the scope and sensitivity of electroanalytical methods.

The modified carbon-based electrode showed good electrocatalytic activity for the oxidation of pharmaceutical samples and it provides greater sensitivity and selectivity with low detection limits and makes this method very able for accurate determinations in pharmaceutical formulation.

Finally, this review demonstrates that carbon-based electrodes can be applied to determine and give comparable results to those obtained by more expensive, time-consuming laboratory techniques.

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