

Research Article

Study of Electrochemical Behavior of Drug Interaction Between Azithromycin and Hydroxychloroquine on Carbon Paste Modified Metal Film Electrode and Local Clay

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Abstract

In this study, a carbon graphite-clay paste electrode (CPEA) was proposed to study the electrochemical behavior of drugs such as azithromycin (AZI) and hydroxychloroquine (HYC). The electrochemical analysis was carried out by cyclic voltammetry (VC) in the potential range [-0.03; 0.35 V], in a phosphate buffer solution (0.1 M; pH = 6.4). It is in this logic that before the elaboration of the carbon graphite-clay composite, the clay powder was prepared and its structural and textural properties were examined by X-ray Diffraction (XRD), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM). The results indicate that the electrode was effectively modified. The electrode was then subjected to electroanalysis at the same concentrations (3 mM) for individual and combined AZI, HYC, and AZI+HYC. However, in the presence of analyte, the phenomena are irreversible, with oxidation phenomena dominating. The electroactivity of the drugs used concerns the hydroxyl groups, observed around 0.18 V. Furthermore, an interaction study in the analytical application was conducted and it was found that the electroanalytical method used can be well adopted for the simultaneous electrochemical detection of HYC and AZI.

Keywords

Graphite, Clay, Azithromycin, Hydroxychloroquine, Electroanalysis

1. Introduction

The risk of drug interactions exists, but today, no recommended course of action is recommended [1, 2], which is the origin of drug-induced iatrogenesis [3, 4]. If we have reached this point today, it is because of our irresponsible behavior regarding the handling of medications, which we have not respected to its proper value, without however taking into account interaction

mechanisms, synergistic effects, or antagonistic actions. The risk that we are exposing the patient to is such that the drug combination in question should not be prescribed; one of the drugs may oppose the action of another or modify the way in which the latter is absorbed and eliminated by the body [5]. If a drug prevents the absorption or action of another, the latter may not show

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Received: 8 July 2025; **Accepted:** 18 July 2025; **Published:** 27 October 2025



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any effectiveness [6]. It is imperative to prescribe another drug of the same class or of another class not exposing to this risk of interaction. The risk of drug interactions is a major health problem [7-9], can lead to the modification of the functioning of the body [10], modification of the activity of enzymes, enzyme inhibitor [11, 12], liver diseases, cardiovascular disorders [13-15], premature death of cells, disorders of the nervous system [16], destroys vital functions, cardiomyopathy [17]. The desire to solve this kind of general problems is marked both by a notion of time and the good understanding of the mechanisms involved in the pharmacology of drugs, even with new drugs. In practice, the use of drugs is advised before prescribing several drugs at the same time [18, 19]. Thus, it is important to develop methods that meet the growing demand and allow efficient analysis and study to identify the potential safety of using these drugs against all kinds of diseases. These methods must be simple and sensitive while allowing the determination of the electrochemical behavior of these drugs. In general, electrochemical sensors using cyclic voltammetry have good characteristics, namely good sensitivity, a fast response, lower cost, quick implementation, and no prior preparation of the analyte is required. Moreover, other techniques are employed for the detection of azithromycin and hydroxychloroquine, namely high-performance liquid chromatography and capillary electrophoresis, but they are very costly and difficult to implement. The aim of this work is to study the effectiveness of cyclic voltammetry on a clay-modified carbon paste electrode, for the detection of the electrochemical behavior of the combination of the drugs azithromycin and hydroxychloroquine and finally proposed a reaction mechanism by the combination of these drugs.

2. Material and Methods

2.1. Material and Chemicals Reagents

The clay material used in this work was the subject of previous work [20-22]. The reagents used in this work are analytically reliable, therefore have not undergone any prior purification. The binder used (paraffin oil) was supplied by the firm Sigma-Aldrich. Azithromycin and Hydroxychloroquine were supplied by Riedel-de Haen. Graphite carbon powder and paraffin oil were purchased from the chemistry laboratory of the University of Maroua in Cameroon. All solutions were prepared with distilled water.

2.2. Characterization Techniques

Information regarding the morphology of modified carbon paste powder was achieved by using a Hitachi (Japan) S-3000H electron microscope at an accelerating voltage of 15 kV which was performed using carbon tape. The absorption

bands of modified electrodes were performed using FT-IR by using the KBr method in which pellet were homogenized by grinding of powder mixture of KBr and MSB, hard-pressed using SHIMADZU MHP-1 hand press. The measurements recorded in IR range of 400-4000 cm^{-1} with 45 scan which was done with the aid of SHIMADZU 8400S FT-IR instrument. In order to determine the mineralogical composition of modified electrode, X-ray diffraction of material powder were recorded using Bruker D8 Advance X-ray diffractometer with $\text{Cu K}\alpha$ ($\lambda = 1.5405 \text{ \AA}$) radiation at diffraction angle of 2θ between $10^\circ - 50^\circ$.

Electrochemical experiments were conducted using a voltalab potentiostat (PGSTAT 100 model, Eco Chemie B. V, Utrecht, The Netherlands) controlled by the voltalab master 4 software. A natural clay-modified carbon paste electrode was used as the working electrode (WE); a saturated calomel electrode (SCE) was used as the reference electrode (RE); and a platinum plate was used as the counter electrode (CE). A pH meter (Copenhagen, PHM210, Tacussel, France) was used to adjust the pH values.

2.3. Preparation of the Working Electrode

Procedure

The working electrode used in this work is a carbon paste electrode (CPE) which will be prepared by mixing graphite carbon powder, clay, and paraffin oil (binder) using a two-step procedure [21, 22]. The modified CPE-Clay electrode is prepared by manually mixing clay powder and graphite powder in a mass ratio of 50%-50% to obtain a homogeneous powder. Paraffin oil will then be added dropwise while stirring until a paste is obtained. Finally, ethanol will be added to the mixture in an appropriate amount as an inert volatile solvent, and the resulting mixture will be thoroughly homogenized and then left in the air for the solvent to evaporate. The paste is manually inserted into the cylindrical cavity of the electrode body (geometric surface area of the working electrode is approximately 0.126 cm^2). The electrode surface obtained was smoothed with a clean and smooth paper, washed with double-distilled water, and dried at laboratory temperature. Finally, the electrode was transferred into an electrochemical cell, with a capacity of 20 ml, containing a phosphate buffer solution (0.1 M ; $\text{pH} = 6.4$) and the substance to be analyzed. The whole was bubbled with pure nitrogen for 10 min. The working electrode was preconcentrated in the solution containing the analyte at an open circuit. The electrochemical drug detection protocol used in this work is generally structured around three phases: the open circuit accumulation phase of the drugs in an aqueous medium contaminated on the surface of the working electrode, the detection phase and the desorption phase, as illustrated in Figure 1.

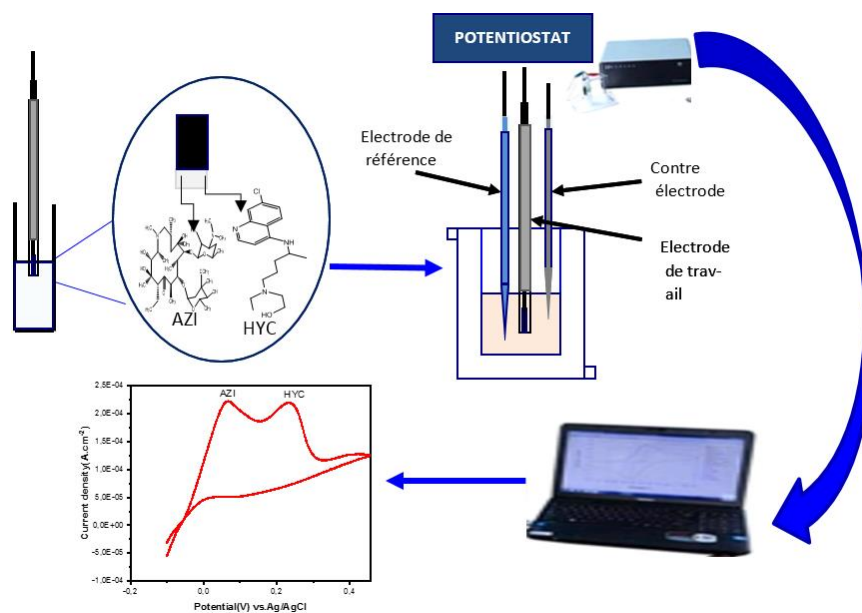


Figure 1. Reaction mechanism of interaction between AZI and HYC.

3. Results and Discussion

3.1. Structural and Mineralogical Analysis of the Modifi Electrode

The DRX patterns of the raw clay and clay-graphite carbon obtained with $\lambda=1.54060 \text{ \AA}$ are shown in Figure 2. The samples show that the clay is mainly composed of phyllosilicate minerals of type 2/1. Impurities such as feldspar (F) and quartz (Q) are also referenced on the diffractograms, as previously reported for similar materials [21]. (Figure 2b) shows that the graphite is well crystallized and has a single intense

line at 26.48° corresponding to the (002) reticular plane of graphitic carbon [22]. It is noted that at 2θ equals 21; 34 and 38.46 are attributed to the presence of Kaolinite (K). The position of the diffraction peak of 2θ equals 5.81; 12.09; 19.96 and 45.42 are diffraction characteristic peaks attributed to montmorillonite (Mt) [23-25]. It is observed that the characteristic peak of Feldspar and Quartz disappear when the clay is modified by graphite carbon, due to the interfacial interactions between the functional groups present on the surface of the clay and the graphite carbon, which suggests that the carbon paste is well modified by clay.

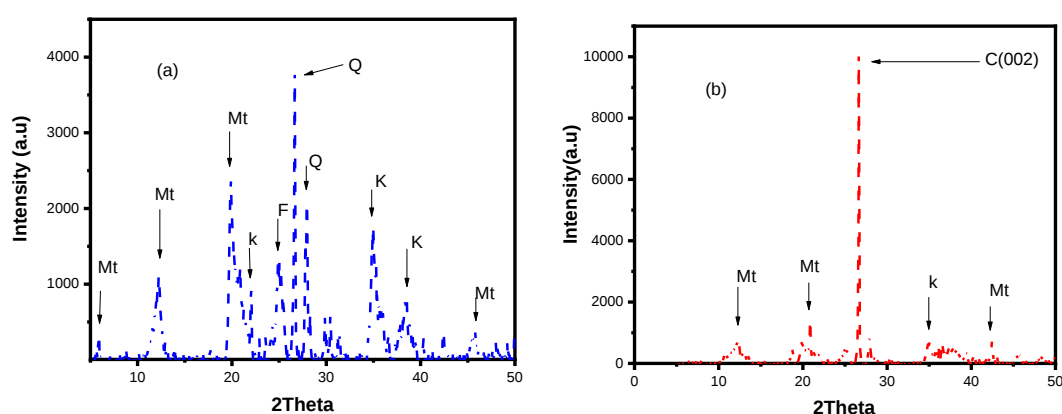


Figure 2. XRD patterns of different electrodes: (a) Clay, (b) CPEA.

3.2. Functional Analysis of the Modified Electrode

The figure below shows the spectra of the FTIR analysis. The different characteristic graphite-clay absorption bands recorded between 400 - 4000 cm^{-1} shows, the band located in the interval 3572-3650 cm^{-1} with a less intense peak, correspond to the elongation vibrations of the OH groups of the octahedral layer of clay material, however, then we notice that

at 1657 cm^{-1} indicates the OH group located in the interlayer spaces. The less intense band located in the interval 1008-1100 cm^{-1} observed corresponds to the valence vibration of Si-O in the tetrahedral layer [26]. The band recorded around 908 cm^{-1} is attributed to the AL-OH group. The band located in the interval 493 cm^{-1} observed corresponds to the valence vibration of free Si-O-AL. The adsorption band located in the range 2351-2164 cm^{-1} is attributed to the conjugate elongation of the C=C bond related to the graphite structure [27, 28].

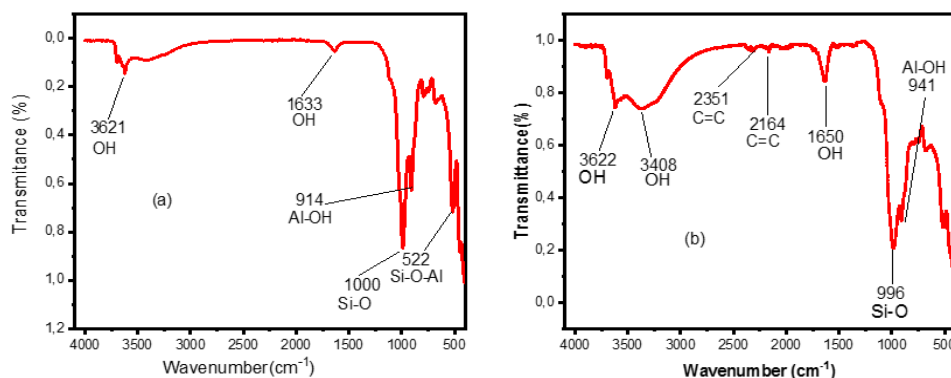


Figure 3. Infra-Red spectra: (a) Clay, (b) CPEA.

3.3. Morphological Analysis of the Modified Electrode Surface

The surface morphology of the raw clay and clay-carbon graphite particles were observed by scanning electron microscopy (SEM). Figure 4 below shows the surface morphology of the clay-modified carbon paste electrode, it shows

an agglomerate of particles of various sizes arranged with a graphitic structure composed of sheets, the raw clay shows the organization of the particles in the form of an assembly of aggregates of micrometric dimensions. The presence of hexagonal shaped particles is noticeable which can be attributed to the quartz particles.

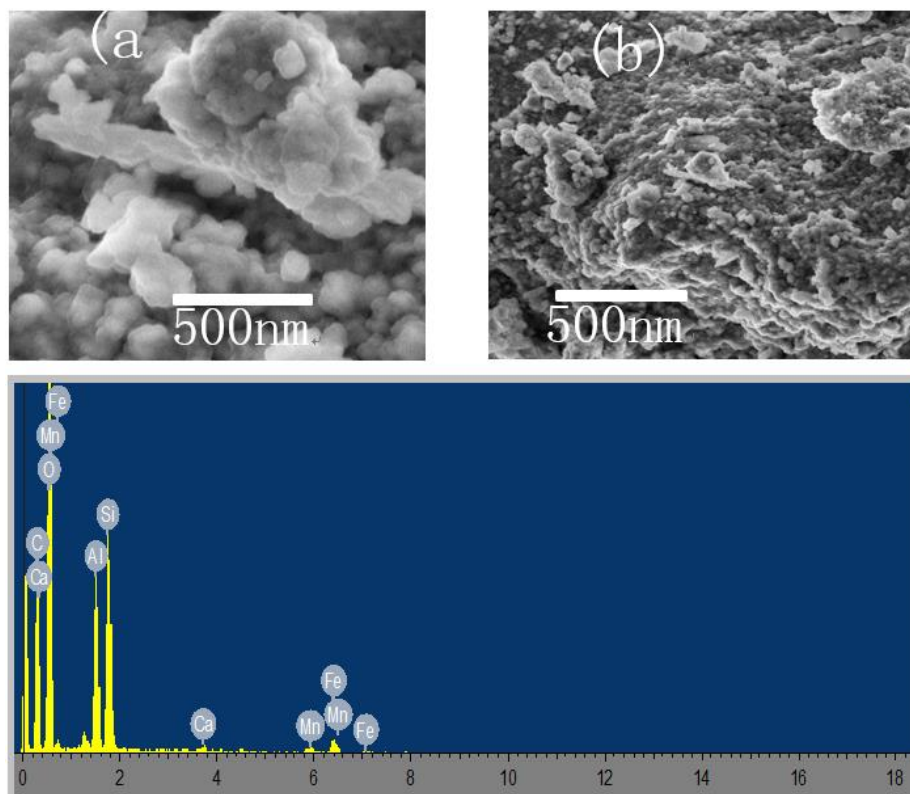


Figure 4. SEM images of (a) Clay, (b) CPEA,

3.4. Application

3.4.1. Electrochemical Behavior of Azithromycin on Graphite-Carbene Clay

Figure 5 below shows the study of the behavior of the CPEA electrode with respect to azithromycin (3mM) by cyclic voltammetry in phosphate buffer medium (pH=6.4), in the potential range $[-0.03; +0.35]$ and with a scanning speed equal to 100 mV/s. It appears that this electrode is electroactive in the presence of azithromycin because the cyclic voltammetric measurement shows a single anodic peak cur-

rent, namely 0.18 V, corresponding to the oxidation of the hydroxyl group to the terminal carbonyl group ($C=O$) [29-31]. The oxidation of the amine function is not observed, which could be explained by a considerable protonation of the $-NH_2$ groups to NH_3^+ . Regarding the detection mechanism of Azithromycin (Figure 5), oxidation concerns the hydroxyl groups. The voltammogram in Figure 5 also shows that the electrode is more favorable to oxidation phenomena (presence of a very intense peak). The figure below shows the detection mechanism of hydroxychloroquine on the surface of the working electrode.

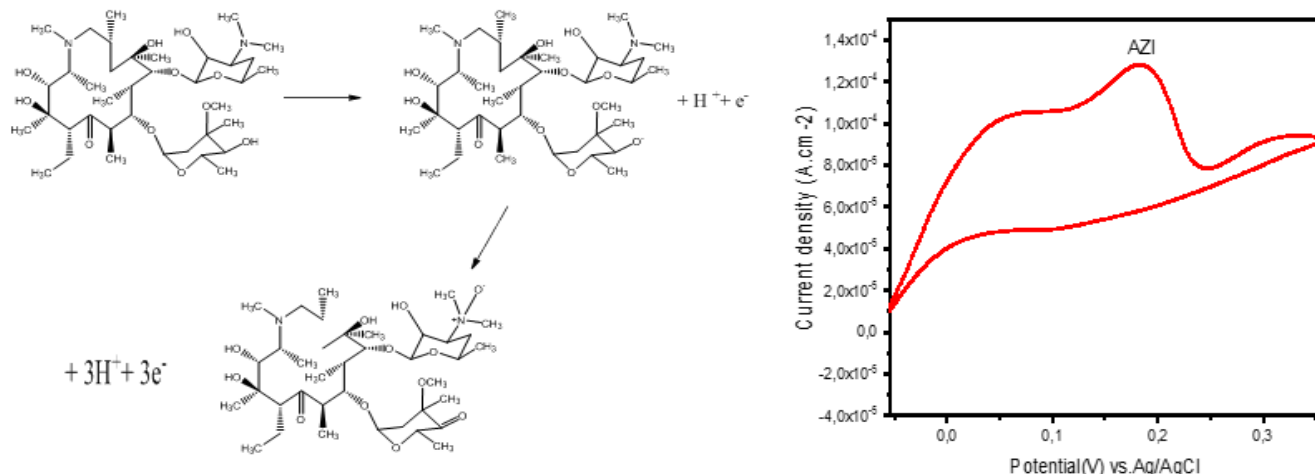


Figure 5. Cyclic voltammograms obtained by graphite carbon paste in the presence of 3 mM azithromycin in a phosphate buffer solution (pH=6.4) with a scanning speed of 100 mV/s.

3.4.2. Electrochemical Behavior of Hydroxychloroquine on CPEA

The ability of the proposed electrode to recognize hydroxychloroquine (3mM) was studied by cyclic voltammetry under the same conditions as previously. The Figure below is an illustration. It also emerges with this molecule (hydroxychloroquine) that the electroactivity of the electrode remains preserved with regard to the peak currents. The

voltammogram relating to it shows the presence of an anodic peak current, one of which is around 0.18V corresponding to the oxidation of the alcohol function, in accordance with the work of Raja and Chtaini (2019) [29]. In addition, the voltammogram also shows that the redox phenomena of hydroxychloroquine are irreversible on the surface of the proposed working electrode, under the conditions of the experiment. The figure below presents the mechanism for detecting hydroxychloroquine on the surface of the working electrode.

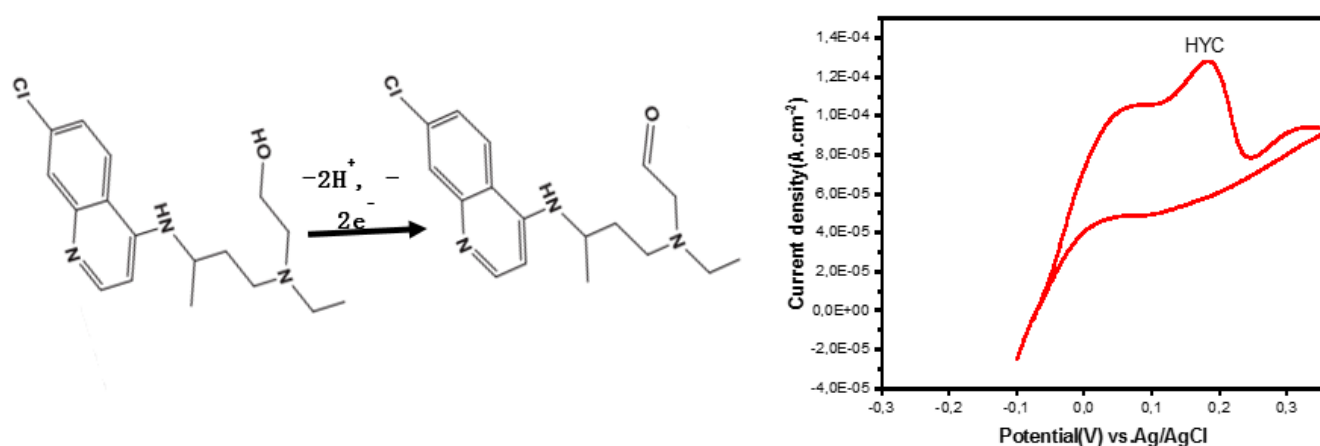
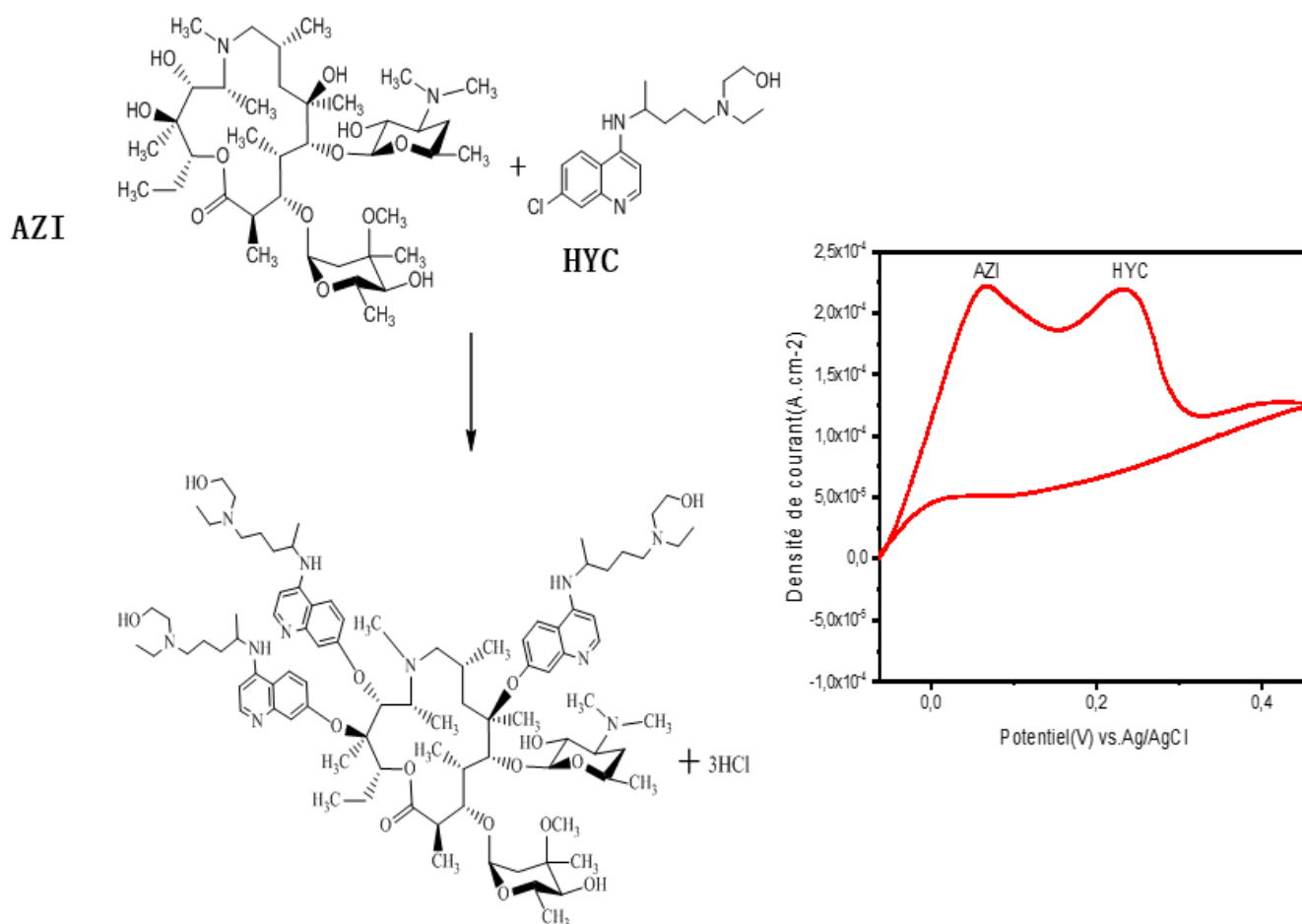


Figure 6. Cyclic voltammograms obtained by graphite carbon paste in the presence of 3mM hydroxychloroquine in a phosphate buffer solution (pH=6.4) with a scanning speed of 100 mV/s.



Mechanism of interaction between AZI and HYC

Figure 7. Cyclic voltammograms obtained by graphite carbon paste in the presence of 3mM azithromycin plus 3mM hydroxychloroquine in a phosphate buffer solution (pH=6. 4) with a scan rate of 100 mV/s.

3.4.3. Effect of the Combination of Different Molecules

The electrochemical behavior of a mixture of AZI and HYC on CPEA in phosphate buffer medium (pH=6. 4), in the potential range [-0. 06; +0. 45] and with a scanning speed equal to 100 mV/s. We note the presence of 2 anodic peaks, respectively at 0. 06 V and 0. 23 V, attributed to the oxidation of AZI and HYC. This shows that the CPEA electrode has good stability, good selectivity, good reproducibility and good feasibility for the simultaneous detection of AZI and HYC in the presence of different interfering species. By addition, the voltammogram presenting the electroanalysis of the combination of the two drugs shows the potential has experienced a slight shift for the two drugs but the peak current related to it is very pronounced compared to that found in the case of the electroanalysis of AZI and HYC alone. This increase in current density at the electrode surface accounts for the increase in affinity between the mixture of the two drugs and the surface of the proposed electrode. This increase would be a consequence of reactions between the two mole-

cules in the electrolytic solution. It is therefore of clear interest to use these drugs in combination. In view of the different electrochemical responses obtained, it would be advisable to use the AZI+HYC combination. Balanced equation of the reaction

Conclusion

The objective of this work is to combat the risk of drug interactions and to study the effectiveness of cyclic voltammetry on a clay-modified carbon paste electrode for the detection of the electrochemical behavior of the combination of the drugs azithromycin (AZI) and hydroxychloroquine (HYC) and finally proposed a reaction mechanism of the combination of these drugs. The analyses showed that the electrode is indeed modified and has physicochemical properties allowing it to interact with other molecules in solution. The electrochemical behavior of each active drug is studied on the surface of the CPEA electrode and also in a combined manner. It appears that the prepared clay-modified carbon paste electrode exhibits a good electrochemical response. This work could open a new avenue to combat the risk of drug interactions and assess the avoidable risk of drug-induced iatrogenesis associated with certain drug combinations.

Acknowledgments

The outcome of this work finds satisfaction in the support granted by the Analytical Chemistry Laboratory of the University of Yaoundé I (Cameroon), the Council for Scientific and Industrial Research (CSIR), the World Academy of Sciences for Advancement of Science in Developing Countries (TWAS).

Conflicts of Interest

The authors declare no conflicts of interest.

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