e-ISSN: 2687-6698 **Review**

Turkish Journal of Analytical Chemistry
www.turkjac.org
2019

A review on recent electroanalytical methods for the analysis of antiviral COVID-19 drugs

Deniz Emre[1], Nuran Özaltın[2], Selehattin Yılmaz[3]*

[1]Çanakkale Onsekiz Mart University, School of Health, Pharmacy Services Program 17100 Çanakkale, Turkey
[2]Hacettepe University, Faculty of Pharmacy, Department of Analytical Chemistry, 06100, Ankara, Turkey
[3]Çanakkale Onsekiz Mart University, Faculty of Science and Arts, Department of Chemistry, 17100 Çanakkale, Turkey

Abstract

Currently, there are no specific drugs for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, designated as coronavirus disease 2019 (COVID-19). Several therapeutic options, including antiviral, antithrombotic, immunosuppressive, and anti-rheumatic drugs, are researched worldwide. Analytical methods are needed in every step of the innovation, research, development, and manufacturing process of pharmaceuticals. Therefore, new analytical methods for pharmaceuticals are developed and validated increasingly over time. In this review, recent reports on electroanalytical techniques for the determination of selected COVID-19 drugs, favipiravir (FAV), remdesivir (REM), lopinavir (LOP) / ritonavir (RIT), hydroxychloroquine (HCQ), chloroquine (CQ), ribavirin (RIB), and sofosbuvir (SOF) were emphasized. Electroanalysis of antiviral active pharmaceutical ingredients carried out at various modified or non-modified electrodes by cyclic voltammetry (CV), linear sweep voltammetry (LSV), differential pulse voltammetry (DPV), square wave voltammetry (SWV), square-wave adsorptive stripping voltammetry (SWAdSV), differential pulse stripping voltammetry (DPSV); adsorptive stripping differential pulse voltammetry (AdSDPV), chronocoulometry (CC) and chronoamperometry (CA) were compiled from the literature. The effects of supporting electrolyte and pH on the current and potential of the analytical signal were evaluated. Scan rate results obtained by the CV method showed whether the redox process of the drug active ingredient diffusion or adsorption controlled at the electrode used in the selected solvent-supporting electrolyte and pH systems. Linearity range and the limit of detection (LOD) of applied electroanalytical methods were compared by combining the results obtained from drug active ingredients given in references.

Keywords: Antiviral drugs, pandemic, coronavirus, Covid-19, analysis, determination, electroanalytical methods

1. Introduction

There are no specific drugs and tests for the treatment of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, designated as the COVID-19 [1]. Repurposing (or repositioning) of existing drugs, such as antivirals for other viruses, anti-rheumatics, corticosteroids, anticoagulants, and other drugs have been used for COVID-19 treatment [2-4].

Although pharmacopeias include many standard methods of analysis, they do not include all pharmaceutical substances. Therefore, developing and validating new analytical methods for pharmaceutical analysis is always needed. This approach makes numerous studies in the literature in a short period, which is hard to follow all of them regularly. That is why reviews are useful; they provide an overview of many methods in a single article, as well as suggest future research directions [5].

After brief information on COVID-19, existing COVID-19 drug regimens, and mechanisms of drug action; this review is focused on recent electroanalytical methods for the analysis of antiviral COVID-19 drugs.

1.1. Coronavirus Infection (COVID-19)

COVID-19 disease, which is caused by a new coronavirus called SARS-CoV-2, is identified by the World Health Organization (WHO) on 31 Dec 2019, following a cluster of case reports on viral pneumonia in Wuhan, China. In a short time, the disease has spread worldwide, and WHO declared the COVID-19 pandemic [6-9].

Citation: D. Emre, N. Özaltın, S. Yılmaz, A review on recent electroanalytical methods for the analysis of antiviral COVID-19 drugs, Turk J Anal Chem, 3(1), 2021, 1-8.

https://doi.org/10.51435/turkjac.935765

***Author of correspondence:** seletyilmaz@hotmail.com
Tel: +90 286 218 00 18
Fax +90 286 218 05 33
Received: May 10, 2021
Accepted: June 06, 2021

According to WHO COVID-19 Dashboard, as of 6 May 2021, there have been 155,506,494 confirmed cases of COVID-19, including 3,247,228 deaths worldwide reported to WHO, and as of 4 May 2021, a total of 1,170,942,729 vaccine doses have been administered. There are no specific drugs for the treatment of COVID-19 but, several APIs, including REM, LOP + RIT combinations, CQ, and HCQ, were suggested in the WHO's Solidarity Therapeutics Trial [6,7,10-12]. Despite the initial reports of success, a recent interim report released by the WHO's Solidarity Therapeutics Trial concluded that REM, HCQ, LOP + RIT, and interferon regimens have little or no effect on 28-day mortality or the hospitalization course of COVID-19 patients and some APIs are under clinical trials [10-14].

Coronaviruses are single-stranded RNA viruses. Six types of coronaviruses, which cause infection in humans, have been reported since the 1960s. For example, SARS-CoV-2 is a type of coronavirus that causes COVID-19. This respiratory illness is defined as various known symptoms containing cough, fever, difficulty breathing, fatigue, conjunctivitis, sore throat, headache changes in the sense of taste and smell. A few antiviral drugs are approved for different infections, or new alternative APIs are under trials for COVID-19 treatment [6,15-22].

1.2. COVID-19 Drugs

SARS-CoV-2 has high contagiousness that causes a considerable risk for the health system. Therefore, many studies are undergoing on a few antiviral drugs, which have been approved for various infections, and tested in different countries [6,9,15-22]. Analytical methods play an important role in these studies, and electroanalytical methods are also of great importance too. A list of some electroactive antiviral compounds used for the treatment of COVID-19 was given in Table 1.

1.3. General information on selected electroactive antiviral Covid-19 drugs

General information on COVID-19 drugs selected for this review is summarized below.

1.3.1. Favipiravir (FAV)

FAV (6-fluoro-3-hydroxy-2-pyrazincarboxamide) is an inhibitor of RNA replication from an RNA template catalyzed by RNA polymerase enzyme [1]. FAV was approved as an antiviral for influenza viruses (avian flu and others) in Japan in 2014. It has been used to treat COVID-19 disease [1,6,23].

1.3.2. Remdesivir (REM)

REM is a new antiviral drug belonging to the class of nucleotide analogues [24,25]. The clinical trials have confirmed the efficiency of REM [26,27]. It manifested exclusive efficiency and activity against COVID-19 in patients with mild and moderate symptoms. It was the first EU-approved drug against COVID-19 [27-31]. Moreover, as it contains a nitrile group, it may show high toxicity if taken in excess [32-35]. REM has been previously administered to West African Ebola virus patients [27]. The mechanism of action of REM is based on viral RNA-dependent RNA polymerase inhibition. REM is a phosphoramidate prodrug of an analogue of adenine-C-nucleoside structure. REM is metabolized into its active form, which is a competitive inhibitor of RNA synthesis [35].

1.3.3. Lopinavir + Ritonavir (LOP + RIT)

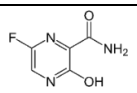
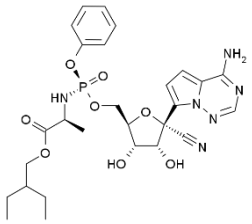
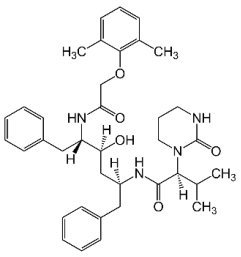
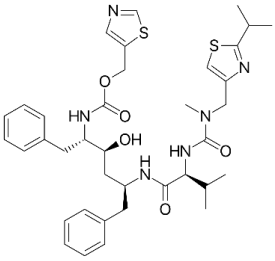
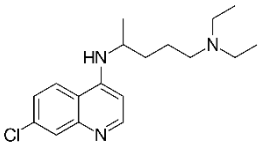
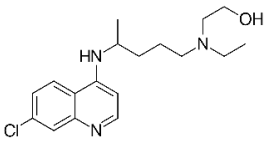
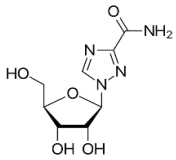
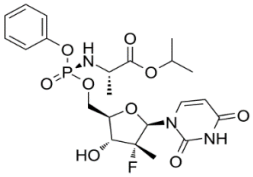
LOP + RIT is an inhibitor of the human immunodeficiency virus (HIV) protease, whose main structure is different from the SARS-CoV-2 counterpart (3CLpro) [26,27,32]. This state would affect the inhibition efficiency of LOP+RIT and raise doubt on the efficacy of LOP + RIT for COVID-19 treatment [26,27,36,37], and WHO has discontinued LOP + RIT use in COVID-19 treatment [2,38].

1.3.4. Hydroxychloroquine (HCQ) and Chloroquine (CQ)

HCQ and CQ are used in the treatment of malaria, discoid lupus erythematosus, and rheumatoid arthritis. In addition, they have been used as antivirals in the treatment of COVID-19 disease [7, 39-41]. HCQ and CQ were thought to be inhibiting the pre-entry step of the viral cycle by interfering with viral particles binding to their cellular cell surface receptors. It was also thought that the intracellular site of SARS-CoV-2 budding was determined by the localization of its membrane M proteins that accumulate in the Golgi complex beyond the site of virion budding, suggesting a possible action of HCQ or CQ at this step of the replication cycle of the virus [7]. However, according to a study on mortality outcomes with HCQ in COVID-19, it is found that HCQ is associated with increased mortality in COVID-19 patients. Also, there is no benefit of CQ [13]. Therefore, WHO has discontinued HCQ and CQ use in COVID-19 treatment [2,38]. Nowadays, in some countries such as Turkey, HCQ use in COVID-19 treatment was discontinued [42].

HCQ had been previously used as an antiviral agent in COVID-19 treatment [7], and has been discontinued nowadays [2,13,38]. But, HCQ has been analyzed by electroanalytical methods recently [39-41]. These methods can be used in further studies, such as toxicological studies on patients who had used HCQ in the past. Therefore, electroanalytical studies on HCQ are included in this review.

Table 1. Antiviral COVID-19 drugs included in this review

Active pharmaceutical ingredient (API)	Therapeutic group	Mechanism of action	Chemical structure	References
FAV	Antiviral	Viral RNA polymerase inhibitor		[6,23]
REM	Antiviral	Viral RNA polymerase inhibitor		[24,25]
LOP + RIT	Antiretroviral	Protease inhibitor	 LOP  RIT	[26,27]
CQ, HCQ	Antirheumatic and antiviral	Cytokine storm inhibitor, viral-cellular binding inhibitor, and viral replication inhibitor	 CQ  HCQ	[7,38-42]
RIB	Antiviral	Viral RNA polymerase inhibitor		[4]
SOF	Antiviral	Viral RNA polymerase inhibitor		[4]

1.3.5. Ribavirin (RIB)

Some nucleotide analogues terminate RNA synthesis catalyzed by polymerases of coronaviruses. Computational chemistry studies, including sequence analysis, modeling, and molecular docking experiments, showed that some nucleotide analogue antiviral drugs can be used to prevent viral replication in infected cells. RIB is one of the RNA-dependent RNA polymerase enzyme inhibitors, which is used for the treatment of hepatitis C virus infections. RIB can also be used against other RNA viruses, such as zika virus and coronaviruses [4].

1.3.6. Sofosbuvir (SOF)

SOF is another nucleotide derivative that is used against Hepatitis C Virus and also SARS-CoV-2. SOF competes with physiological nucleotide for RNA-dependent RNA polymerase enzyme active site, competitively inhibits viral RNA polymerase, and by the way, it prevents viral replication of SARS-CoV-2 in infected cells [4].

2. Electrochemical behavior and determination of antiviral COVID-19 drugs

This current review reported the most recent and relevant literature dealing with the electroanalytical determination of COVID-19 antiviral drugs in pharmaceutical preparations and biological samples (such as urine and plasma). Thus, selective and sensitive electroanalytical methods are needed for these complicated samples [1].

Recent developments in technology make electroanalytical determinations more selective, sensitive, rapid, and easy than other methods and applicable for most pharmaceutical and chemical analysis fields. As a result, electrochemical methods

nowadays enable trace analysis for pharmaceuticals with a sufficient degree of precision, accuracy, selectivity, sensitivity, and reproducibility.

Electroanalytical determination of drugs can be used for understanding their pharmacokinetic properties (adsorption, distribution, metabolism, and elimination). In addition, the determination of APIs in biologic samples is useful for new drug development, bio-equivalence, toxicology, and drug-monitoring studies [43,44].

In this review, various electro-analytical methods for the determination of COVID-19 drugs in different samples available literature are summarized as below:

2.1. FAV

Investigation of the literature revealed that three studies had been carried out for the quantification of FAV by High-Performance Liquid Chromatography (HPLC) with ultraviolet (UV) detector [6,45], spectrofluorimetric [6,46], and electroanalytical methods [6]. Electroanalytical techniques are versatile analytical techniques that can easily solve many problems of pharmaceutical interest. Varieties of techniques are available to researchers to study the electrochemistry of electroactive species in solution. Particularly voltammetry is a practical electroanalytical technique that offers high sensitivity, selectivity, precision, and accuracy, a wide linear range, and low-cost instrumentation and time.

The electrochemical behavior and determination of FAV were carried out first time in pharmaceutical and biological samples at Boron Doped Diamond (BDD) electrode by CV and SWAdSV [6]. Some of the analysis parameters, such as concentration range and LOD values, were given in Table 2.

2.2. REM

Electroanalytical methods studied on similar molecular structures with the analyte can be useful when the analyte does not have a validated electroanalytical method. A theoretically evaluated electrochemical determination of REM by correspondent mathematical model analysis, made by linear stability theory and bifurcation analysis, has been studied on an anodic process using a Squaraine Dye-Ag_2O_2 composite. In this theoretical study, it was reported that the composite has electroanalytical efficiency as an electrode modifier [25]. The calculated LOD value was given in Table 2.

2.3. LOP + RIT

Simultaneous determination of RIT and some other antivirals in human plasma, using HPLC with combined ultraviolet absorbance and electrochemical (potentiometric) detector was studied [47].

Electrochemical Impedance Spectroscopy (EIS) was studied with nanomaterial-modified biosensors, which can be used in biosensing probes to determine the interaction between SARS-CoV-2 spike protein and drugs. SARS-CoV-2 enters human cells by binding its spike protein to the cell expressing angiotensin-converting enzyme 2 (ACE2). Some ACE2 inhibitors, as ramiprilat and perindoprilat, are found to be effective for inhibition of spike protein-ACE2 binding. EIS is concluded to be useful for developing biosensors for screening of modulators for S-protein-ACE2 binding [11]. A similar screening assay based on EIS was developed for the determination of protease inhibitors at picomolar levels, including LOP + RIT. The method was based on the immobilization of the thiol terminated ferrocene (Fc)-pepstatin conjugate on a single-walled carbon nanotube/gold nanoparticle modified gold electrode. The estimated inhibition constant (Ki) was reported for LOP + RIT as Ki = 20 ± 3 pmol/L [48]. A similar assay can be studied for SARS-CoV-2 protease inhibitors. Some of the analysis parameters, such as concentration range and LOD values, were given in Table 2.

2.4. HCQ

The sensitive electrochemical sensor was improved by the modification of a glassy carbon electrode (GCE) with a new Schiff base [41].

The electrochemical properties of HCQ in the existence of uric acid (UA) at the surface of the modified electrode were studied by the DPV technique. In addition, the effect of pH, scan rate on the current and potential signal of HCQ was studied. Finally, the nanosensor was economically developed for the analysis of actual samples [41]. So far, some electrochemical techniques applied for the analysis of HCQ and CQ are summarized in Table 2 [40,49-51].

CV and DPV methods containing accumulation and stripping steps were developed for the determination of CQ on modified carbon paste electrodes. Accumulation and trace measurement were carried on dsDNA modified carbon paste surface, which allowed a preconcentration step for CQ. Modification of the carbon paste electrode achieved higher sensitivity compared with the bare surface. The linear range was 1.0×10^{-7} - 1.0×10^{-5} mol/L and LOD was 3.0×10^{-8} mol/L at the dsDNA-modified electrode. The method was applied on serum, without sample pretreatment [52,53].

CV and DPV methods were developed for the determination of CQ using GCE electrode modified with reduced graphene oxide on tungsten disulfide WS2 quantum dots. A hydrothermal method was used for the WS_2 quantum dots synthesis.

Table 2. Summary of electrochemical studies of antiviral COVID-19 drugs

Drug name	Linear range	Limit of detection (LOD)	Method	Application media	Ref.
FAV	0.01 - 0.10 µg/Ml (6.4×10^{-8} - 6.4×10^{-7} M)	0.0028 µg/mL (1.8×10^{-8} M)	CV and SW-AdSV-BDD Electrode	Pharmaceutical tablets, Human urine	[6]
FAV	0.10 - 20.00 µg/mL (6.4×10^{-7} - 1.3×10^{-4} M)	0.023 µg/mL (1.5×10^{-7} M)	CV and SW-AdSV-BDD Electrode	Pharmaceutical tablets, Human urine	[6]
REM	(Theoretical study without experimental results)	(Theoretical study without experimental results)	EO-Squaraine Dye -Ag_2O_2 Composite	(Theoretical study without experimental results)	[25]
RIT	250 - 5000 ng/mL	12 ng/mL	HPLC-EC	Human plasma	[47]
LOP + RIT	20 - 1000 pmol/mL	10 pmol/mL	EIS- SWCNT/AuNP-Modified Gold Electrode	Clinical drug capsules	[48]
HCQ	2.00×10^{-5} - 5.00×10^{-4} mg/mL	11.29 mg/mL	DPV-GCE	Malaria drug (Plaquenil)	[40]
CQ	0.068 - 6.88 mg/mL	0.01 mg/mL	DPV-$Cu(OH)_2$ Nanowire-Modified CPE	Pharmaceutical tablet	[49]
HCQ	0.10 - 1.90 mmol/L	0.06 mmol/L	SWV-Cathodically Pretreated BDD Electrode	Spiked human blood serum	[50]
HCQ	0.01 - 0.25 µmol/L	2.00 nmol/L	SWV- Cathodically Pretreated BDD Electrode	Commercial pharmaceutical samples	[50]
HCQ	0.10 - 10.0 µmol/L	0.03 µmol/L	SWV-dsDNA/CPE	Commercial pharmaceutical samples	[50]
HCQ	0.13 - 13.30 µmol/L	0.02 µmol/L	SWV-CuNW/CPE	Commercial pharmaceutical samples	[50]
HCQ	1.0×10^{-5} - 1.0×10^{-2} mol/L 1.0×10^{-6} - 1.0×10^{-2} mol/L	7.90×10^{-6} mol/L 5.00×10^{-6} mol/L	ISE- PME and Modified-CPE	Pharmaceutical preparations and human urine	[51]
CQ	1.0×10^{-7} - 1.0×10^{-5} M	3.0×10^{-8} M	CV and DPSV- CPE modified with dsDNA	Human serum	[52,53]
CQ	0.5 - 82 µM	40 - 120 nM	CV and DPV- Modified GCE with rGO/ WS_2 Quantum Dots	Human serum and pharmaceutical formulations	[52,54]
HCQ	5.7×10^{-8} - 1.0×10^{-4} M	6.0 nM	AdSDPV,CV,CC and CA-MWCNTs/CPE	Pharmaceutical formulations and biological fluids	[52,55]
RIB	10.0-7.5×10^2 ng/mL	No data available	CV-APBA/ERGO/GCE	Pharmaceutical injections	[56]
RIB	1.0×10^{-10} - 2.0×10^{-7} mol/L	2.02×10^{-10} mol/L	SWASV-HMDE	Pharmaceutical dosage form, urine, and serum	[57]
SOF	1 - 400 nM	0.36 nM	CV and DPV-N,S@GQDs Electrode	Human plasma	[58,59]

DPV: Differential Pulse Voltammetry; SWV: Square Wave Voltammetry; CV: Cyclic Voltammetry; SWAdSV: Square-Wave Adsorptive Stripping Voltammetry; SWASV: Square-Wave Adsorptive Stripping Voltammetry; DPSV: Differential Pulse Stripping Voltammetry; AdSDPV: Adsorptive Stripping Differential Pulse Voltammetry; CC: Chronocoulometry; CA: Chronoamperometry; EO: Electrochemical Oscillations; ISE: Ion Selective Electrode, HPLC-EC: High Performance Liquid Chromatography-Electrochemical Detector; EIS: Electrochemical Impedance Spectroscopy; BDD: Boron-Doped Diamond; CPE : Carbon Paste Electrode; GCE : Glassy Carbon Electrode; PME: Polymeric Membrane Electrode; CuNW/CPE: Copper Nanowires/Carbon Paste Electrode; dsDNA/CPE: Double-Stranded DNA/Carbon Paste Electrode; SWCNT/AuNP-Modified Gold Electrode: Single-Walled Carbon Nanotube/Gold Nanoparticle Modified Gold Electrode; APBA/ERGO/GCE: 3-Aminophenylbornic Acid Electrochemically Reduced Graphene Oxide Modified Glassy Carbon Electrode; HMDE: Hanging Mercury Drop Electrode; N,S@GQDs: N,S co-doped graphene quantum dots electrode; CPE modified with dsDNA: Carbon Paste Electrode Modified with Double Stranded Deoxyribonucleic Acid; Modified-GCE with rGO/WS_2QDs: Modified Glassy Carbon Electrode with Reduced Graphene Oxide Layers Containing Tungsten Disulphite Quantum Dots; MWCNTs/CPE : Multiwalled Carbon Nanotubes/ Carbon Paste Electrode

The resulting composite material, containing WS2 quantum dots on reduced graphene oxide sheets, was deposited on a GCE to enhance electroactivity. CQ potential maximum was at 1.2 V (vs. AgCl/Ag) on the modified GCE. The linear range was 0.5 µM - 82 µM for CQ, and LOD was 40 - 120 nM (at S/N = 3). The method was applied to human serum and pharmaceutical formulations [52,54].

The determination of HCQ was carried on AdSDPV with multiwall carbon nanotube-modified carbon paste electrode. CV, CC, and CA were also studied on HCQ. Linear range was 5.7×10^{-8} M - 1×10^{-4} M, and LOD was 6.0 nM (S/N = 3) [52,55].

2.5. RIB

It was reported that RIB was not electrochemically active. Therefore, RIB was determined by an indirect electrochemical method, using boronic acid-functionalized modified GCE. Modification of the GCE was carried out by 3-aminophenylboronic acid-electrochemically reduced graphene oxide. CV reduction peak current of $[Fe(CN)_6]^{3-/4-}$ was measured

before and after the addition of RIB. After the modified GCE was immersed in RIB solution, complexation of RIB with boronic acid groups on the surface of the modified GCE caused steric effects, and CV reduction peak current of $[Fe(CN)_6]^{3-/4-}$ was decreased. The optimal reaction time between RIB and modified GCE surface was reported to be 10 min, pH was 7.5 and temperature was 15 °C. The linear range was 10.0 - 7.5 × 10^2 ng/mL. The developed method was applied on the determination of RIB in an injection and results were reported to be comparable with the standard HPLC method described in the Chinese Pharmacopoeia Commission [56].

SWAdSV was applied for the determination of RIB in pharmaceutical formulations and biological samples (urine and serum). The developed method was based on the reduction of RIB at hanging mercury drop electrode in Britton Robinson buffer at pH 10, after accumulation for 30 s at 50 mV potential, the peak was observed at 880 mV. The linear range was 1.0 × 10^{-10} - 2.0 × 10^{-7} mol/L and LOD was 2.02 × 10^{-10} mol/L [57]. Some of the analysis parameters, such as concentration range and LOD values, were given in Table 2.

2.6. SOF

A molecularly imprinted polymer was proposed for the electrochemical determination of SOF. The sensor was obtained by polymerization of p-amino thiophenol on N,S co-doped graphene quantum dots in the presence of gold nanoparticles to form a gold-sulfur covalent network. It was reported that the quantum dots improved the electron transfer rate, enhanced surface activity, and amplified the signal. DPV and CV were applied with the developed sensor. SOF linear concentration range was found to be 1 - 400 nM, and the LOD was 0.36 nM. SOF spiked human plasma was studied [58,59]. Some of the analysis parameters, such as concentration range and LOD values, were given in Table 2.

3. Conclusions

The main aim of pharmaceuticals is to make humans free from potential illness or prevent them from getting ill. There are no specific drugs against COVID-19. Therefore, drug repurposing is a useful method for COVID-19 treatment. Antiviral drugs, which were used against other viruses with similar mechanisms of viral replication, may also be effective against SARS-CoV-2. Studies in various fields focusing on this approach need electroanalytical methods for antiviral COVID-19 drugs. This review is focused on the electroanalytical methods developed for the analysis of antiviral COVID-19 drugs in pharmaceutical forms and biological samples such as in human serum and urine. The methods studied with various modified or non-modified electrodes were compiled from the literature. Quantitative analysis of antiviral COVID-19 drug active ingredients was investigated in terms of some validation parameters such as linearity range, LOD, and sensitivity. The review also highlights the advantages of the applied electroanalytical techniques. It is concluded that electroanalytical methods and electrochemical sensors offer some unique advantages over other analytical methods, and more electroanalytical studies on antiviral COVID-19 drugs are recommended for further research. Due to the lack of electroanalytical methods for the analysis of antiviral COVID-19 drugs in the literature, this review will shed light on new research studies by giving brief information about existing studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] M.A. Acquavia, L. Foti, R. Pascale, A. Nicolò, V. Brancaleone, T.R.I. Cataldi, G. Martelli, L. Scrano, G. Bianco, Detection and quantification of Covid-19 antiviral drugs in biological fluids and tissues, Talanta, 224, 2021, 121862.

[2] WHO solidarity trial consortium, repurposed antiviral drugs for COVID-19-interim who solidarity trial results, New Engl J Med, 384(6), 2021, 497-511.

[3] S. Dotolo, A. Marabotti, A. Facchiano, R. Tagliaferri, A review on drug repurposing applicable to COVID-19, Brief Bioinform, 22(2), 2021, 726-741.

[4] A.A. Elfiky, Anti-HCV, nucleotide inhibitors, repurposing against COVID-19, Life Sci, 248, 2020, 117477.

[5] S. Ahmed, M.S. Islam, B. Ullah, S. Kanti Biswas, M.A. Samad Azad, M.S. Hossain, A review article on pharmaceutical analysis of pharmaceutical industry according to pharmacopoeias, Orient J Chem, 36, 2020, 01-10.

[6] S. Allahverdiyeva, O. Yunusoğlu, Y. Yardım, Z. Şentürk, First electrochemical evaluation of favipiravir used as an antiviral option in the treatment of COVID-19: A study of its enhanced voltammetric determination in cationic surfactant media using a boron-doped diamond electrode, Anal Chim Acta, 1159, 2021, 338418.

[7] C.A. Devaux, J.-M. Rolain, P. Colson, D. Raoult, New insights on the antiviral effects of chloroquine against coronavirus: What to expect for COVID-19?, Int J Antimicrob Agents, 55, 2020, 105938.

[8] World Health Organization, Questions and Answers: What is COVID-19?, 2020, https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19

[9] C. Sohrabi, Z. Alsafi, N. O'Neill, M. Khan, A. Kerwan, A. Al-Jabir, C. Iosifidis, R. Agha, World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19), Int J Surg, 76, 2020, 71-76.

[10] E. Dong, H. Du, L. Gardner, An interactive web-based dashboard to track COVID-19 in real time, Lancet Infect Dis, 20 ,2020, 533-534.

[11] L.V. Kiew, C.Y. Chang, S.Y. Huang, P.W. Wang, C.H. Heh, C.T. Liu, C.H. Cheng, Y.X. Lu, Y.C. Chen, Y.X. Huang, S.Y. Chang, H.Y. Tsai, Y.A. Kung, PN. Huang, M.-H. Hsu, B.F. Leo, Y.Y. Foo,

C.H. Su, K.C. Hsu, P.H. Huang, C.J. Ng, A. Kamarulzaman, C.J. Yuan, D.B. Shieh, S.R. Shih, L.Y. Chung, C.C. Chang, Development of flexible electrochemical impedance spectroscopy-based biosensing platform for rapid screening of SARS-CoV-2 inhibitors, Biosens Bioelectron, 183, 2021, 113213.

[12] C. Harrison, Coronavirus puts drug repurposing on the fast track, Nat Biotechnol, 38, 2020, 379-381.

[13] C. Axfors, A.M. Schmitt, P. Janiaud, J. Van'T Hooft, S. Abd-Elsalam, E.F. Abdo, B.S. Abella, J. Akram, R.K. Amaravadi, D.C. Angus, Y.M. Arabi, S. Azhar, L.R. Baden, A.W. Baker, L. Belkhir, T. Benfield, M.A.H. Berrevoets, C.-P. Chen, T.-C. Chen, S.-H. Cheng, C.-Y. Cheng, W.-S. Chung, Y.Z. Cohen, L.N. Cowan, O. Dalgard, F.F. De Almeida E Val, M.V.G. De Lacerda, G.C. De Melo, L. Derde, V. Dubee, A. Elfakir, A.C. Gordon, C.M. Hernandez-Cardenas, T. Hills, A.I.M. Hoepelman, Y.-W. Huang, B. Igau, R. Jin, F. Jurado-Camacho, K.S. Khan, P.G. Kremsner, B. Kreuels, C.-Y. Kuo, T. Le, Y.-C. Lin, W.-P. Lin, T.-H. Lin, M.N. Lyngbakken, C. Mcarthur, B.J. Mcverry, P. Meza-Meneses, W.M. Monteiro, S.C. Morpeth, A. Mourad, M.J. Mulligan, S. Murthy, S. Naggie, S. Narayanasamy, A. Nichol, L.A. Novack, S.M. O'Brien, N.L. Okeke, L. Perez, R. Perez-Padilla, L. Perrin, A. Remigio-Luna, N.E. Rivera-Martinez, F.W. Rockhold, S. Rodriguez-Llamazares, R. Rolfe, R. Rosa, H. Røsjø, V.S. Sampaio, T.B. Seto, M. Shehzad, S. Soliman, J.E. Stout, I. Thirion-Romero, A.B. Troxel, T.-Y. Tseng, N.A. Turner, R.J. Ulrich, S.R. Walsh, S.A. Webb, J.M. Weehuizen, M. Velinova, H.-L. Wong, R. Wrenn, F.G. Zampieri, W. Zhong, D. Moher, S.N. Goodman, J.P.A. Ioannidis, L.G. Hemkens, Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials, Nat Commun, 12, 2021, 2349.

[14] H. Pan, R. Peto, Q.A. Karim, M. Alejandria, A.M. Henao-Restrepo, C.H. García, M.-P. Kieny, R. Malekzadeh, S. Murthy, M.-P. Preziosi, S. Reddy, M.R. Periago, V. Sathiyamoorthy, J.-A. Røttingen, S. Swaminathan, Repurposed antiviral drugs for COVID-19 -interim WHO SOLIDARITY trial results, MedRxiv, 2020.

[15] A.R. Fehr, S. Perlman, Coronaviruses: An Overview of Their Replication and Pathogenesis, Methods in Molecular Biology, Editors: H. Maier, E. Bickerton, P. Britton, 2015, 1-23, USA, New-York.

[16] C.C. Lai, T.P. Shih, W.C. Ko, H.J. Tang, P.R. Hsueh, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges, Int J Antimicrob Agents, 55, 2020, 105924.

[17] S.J. Chen, S.C. Wang, Y.C. Chen, Novel Antiviral Strategies in the Treatment of COVID-19: A Review, Microorganisms, 8, 2020, 1259.

[18] Y.A. Helmy, M. Fawzy, A. Elaswad, A. Sobieh, S.P. Kenney, A.A. Shehata, The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control, J Clin Med, 9, 2020, 1225.

[19] B. Udugama, P. Kadhiresan, H.N. Kozlowski, A. Malekjahani, M. Osborne, V.Y.C. Li, H. Chen, S. Mubareka, J.B. Gubbay, W.C.W. Chan, Diagnosing COVID-19, The Disease and Tools for Detection, ACS Nano, 14, 2020, 3822-3835.

[20] Y. Jin, H. Yang, W. Ji, W. Wu, S. Chen, W. Zhang, G. Duan, Virology, Epidemiology, Pathogenesis, and Control of COVID-19, Viruses, 12, 2020, 372.

[21] WHO Coronavirus Disease (COVID-2019) Dashboard, 2021, https://covid19.who.int.

[22] Y. Furuta, K. Takahashi, K. Shiraki, K. Sakamoto, D.F. Smee, D.L. Barnard, B.B. Gowen, J.G. Julander, J.D. Morrey, T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections, Antivir Res, 82, 2009, 95-102.

[23] Y. Du, X. Chen, Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection, Clin Pharmacol Ther, 108, 2020, 242-247.

[24] S. Bagheri Novir, M.R. Aram, Quantum mechanical studies of the adsorption of Remdesivir, as an effective drug for treatment of COVID-19, on the surface of pristine, COOH-functionalized and S-, Si- and Al- doped carbon nanotubes, Physica E, 129, 2021, 114668.

[25] V.V. Tkach, M.V. Kushnir, S.C. Oliveira, J.G. Ivanushko, A.V. Velyka, A.F. Molodianu, P.I. Yagodynets, Z.O. Kormosh, , L.V. Reis, O.V. Luganska, K.V. Palamarek, Y.L. Bredikhina, Theoretical Description for Anti-COVID-19 Drug Remdesivir Electrochemical Determination, Assisted by Squaraine Dye-Ag_2O_2 Composite, Biointerface Res Appl Chem, 11, 2021, 9201-9208.

[26] Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, H. Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19, New Engl J Med, 382, 2020, 1787-1799.

[27] M. Costanzo, M.A.R. Giglio, G.N. Roviello, SARS-CoV-2: Recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus, Curr Med Chem, 27, 2020, 4536-4541.

[28] R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, M.D. Hall, Remdesivir: A Review of its discovery and development leading to emergency use authorization for treatment of COVID-19, ACS Cent Sci, 6, 2020, 672-683.

[29] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. Dezure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, T. Flanigan, Compassionate Use of Remdesivir for Patients with Severe Covid-19, New Engl J Med, 382, 2020, 2327-2336.

[30] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez De Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M.-D. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the Treatment of Covid-19-Final Report, New Engl J Med, 383, 2020, 1813-1826.

[31] S.C.J. Jorgensen, R. Kebriaei, L.D. Dresser, Remdesivir: review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19, Pharmacotherapy, 40, 2020, 659-671.

[32] V. Avataneo, A. De Nicolò, J. Cusato, M. Antonucci, A. Manca, A. Palermiti, C. Waitt, S. Walimbwa, M. Lamorde, G. Di Perri, A. D'Avolio, Development and validation of a UHPLC-MS/MS method for quantification of the prodrug remdesivir and its metabolite GS-441524: a tool for clinical pharmacokinetics of SARS-CoV-2/COVID-19 and Ebola virus disease, J Antimicrob Chemoth, 75, 2020, 1772-1777.

[33] T.P. Sheahan, A.C. Sims, S.R. Leist, A. Schäfer, J. Won, A.J. Brown, S.A. Montgomery, A. Hogg, D. Babusis, M.O. Clarke, J.E. Spahn, L. Bauer, S. Sellers, D. Porter, J.Y. Feng, T. Cihlar, R. Jordan, M.R. Denison, R.S. Baric, Comparative therapeutic efficacy of

remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV, Nat Commun, 11, 2020, 1-14.
[34] C.J. Gordon, E.P. Tchesnokov, E. Woolner, J.K. Perry, J.Y. Feng, D.P. Porter, M. Götte, Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency, J Biol Chem, 295, 2020, 6785-6797.
[35] M. Sisay, Available evidence and ongoing clinical trials of remdesivir: Could it be a promising therapeutic option for COVID-19?, Front Pharmacol, 11, 2020, 1-6.
[36] Q. Wang, Y. Zhao, X. Chen, A. Hong, Virtual screening of approved clinic drugs with main protease (3CLpro) reveals potential inhibitory effects on SARS-CoV-2, J Biomol Struct Dyn. 2020, 1-11, 1817786.
[37] Y.W. Chen, C.P.B. Yiu, K.Y. Wong, Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates, F1000Research, 9, 2020, 129.
[38] WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19, 2020, https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19.
[39] A. Shrivastava, Analytical methods for the determination of hydroxychloroquine in various matrices, Int J Appl Pharm, 12, 2020, 55-61.
[40] M.L.P.M. Arguelho, J.F. Andrade, N.R. Stradiotto, Electrochemical study of hydroxychloroquine and its determination in Plaquenil by differential pulse voltammetry, J Pharmaceut Biomed, 32, 2003, 269-275.
[41] A. Khoobi, S.M. Ghoreishi, M. Behpour, Sensitive and selective determination of hydroxychloroquine in the presence of uric acid using a new nanostructure self-assembled monolayer modified electrode: optimization by multivariate data analysis, Analyst, 139, 2014, 4064-4072.
[42] Republic of Turkey, Ministry of Health, Discontiues hydroxychloroquine treatment in COVID-19 in guide for treatment of adult patients with COVID-19, 2021, https://covid19.saglik.gov.tr/Eklenti/40719/0/covid-19rehberieriskinhastayonetimivetedavipdf.pdf.
[43] J.S. Kang, M.H. Lee, Overview of Therapeutic Drug Monitoring, Korean J Intern Med, 24, 2009, 1.
[44] N.M. Cassiano, V.V. Lima, R.V. Oliveira, A.C. De Pietro, Q.B. Cass, Development of restricted-access media supports and their application to the direct analysis of biological fluid samples via high-performance liquid chromatography, Anal Bioanal Chem, 384, 2006, 1462-1469.
[45] I. Bulduk, HPLC-UV method for quantification of favipiravir in pharmaceutical formulations, Acta Chromatogr, 33, 2020, 209-215.
[46] S.M. Megahed, A.A. Habib, S.F. Hammad, A.H. Kamal, Experimental design approach for development of spectrofluorimetric method for determination of favipiravir; a potential therapeutic agent against COVID-19 virus: Application to spiked human plasma, Spectrochim Acta A, 249, 2021, 119241.
[47] E. Marchei, R. Pacifici, G. Tossini, R. Di Fava, L. Valvo, P. Zuccaro, Simultaneous liquid chromatographic determination of indinavir, saquinavir, and ritonavir in human plasma with combined ultraviolet absorbance and electrochemical detection, J Liq Chromatogr R T, 24, 2001, 2325-2336.
[48] K.A. Mahmoud, J.H.T. Luong, Impedance method for detecting hiv-1 protease and screening for its inhibitors using ferrocene−peptide conjugate/Au nanoparticle/single-walled carbon nanotube modified electrode, Anal Chem, 80, 2008, 7056-7062.
[49] M.H. Mashhadizadeh, M. Akbarian, Voltammetric determination of some anti-malarial drugs using a carbon paste electrode modified with $Cu(OH)_2$ nano-wire, Talanta, 78, 2009, 1440-1445.
[50] P.B. Deroco, F.C. Vicentini, G.G. Oliveira, R.C. Rocha-Filho, O. Fatibello-Filho, Square-wave voltammetric determination of hydroxychloroquine in pharmaceutical and synthetic urine samples using a cathodically pretreated boron-doped diamond electrode, J Electroanal Chem, 719, 2014, 19-23.
[51] M.M. Khalil, Y.M. Issa, G.A. El Sayed, Modified carbon paste and polymeric membrane electrodes for determination of hydroxychloroquine sulfate in pharmaceutical preparations and human urine, RSC Adv, 5, 2015, 83657-83667.
[52] C. Saka, Analytical methods on determination in pharmaceuticals and biological materials of chloroquine as available for the treatment of COVID-19, Crit Rev Anal Chem, 2020, 1-16.
[53] A. Radi, Accumulation and trace measurement of chloroquine drug at DNA-modified carbon paste electrode, Talanta, 65, 2004, 271-275.
[54] M. Srivastava, P. Tiwari, V.K. Mall, S.K. Srivastava, R. Prakash, Voltammetric determination of the antimalarial drug chloroquine using a glassy carbon electrode modified with reduced graphene oxide on WS2 quantum dots, Microchim Acta, 186, 2019, 415.
[55] S.M. Ghoreishi, A.M. Attaran, A.M. Amin, A. Khoobi, Multiwall carbon nanotube-modified electrode as a nanosensor for electrochemical studies and stripping voltammetric determination of an antimalarial drug, RSC Adv, 5, 2015, 14407-14415.
[56] X. Wang, W. Shen, X. Zhang, S. Guo, Y. Gao, X. Li, F. Feng, G. Yang, Indirect Electrochemical Determination of Ribavirin Using Boronic Acid-Diol Recognition on a 3-Aminophenylboronic Acid-Electrochemically Reduced Graphene Oxide Modified Glassy Carbon Electrode (APBA/ERGO/GCE), Anal Lett, 52, 2019, 1900-1913.
[57] A.A.A. Gaber, S.A. Ahmed, A.M.A. Rahim, Cathodic adsorptive stripping voltammetric determination of Ribavirin in pharmaceutical dosage form, urine and serum, Arab J Chem, 10, 2017, 2175-2181.
[58] A.M. Mahmoud, M.M. El-Wekil, M.H. Mahnashi, M.F.B. Ali, S.A. Alkahtani, Modification of N,S co-doped graphene quantum dots with p-aminothiophenol-functionalized gold nanoparticles for molecular imprint-based voltammetric determination of the antiviral drug sofosbuvir, Microchim Acta, 186 ,2019, 617.
[59] O. Selcuk, Y. Demir, C. Erkmen, S. Yıldırım, B. Uslu, Analytical methods for determination of antiviral drugs in different matrices: recent advances and trends, Crit Rev Anal Chem, 2021, 1-32.