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A Subject Review on a Some Analytical Methods for the Determination of Chloroquine and Hydroxychloroquine Drugs

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Abstract

Chloroquine and Hydroxychloroquine drugs are widely prescribed for malaria disease. Since the end of 2019, humans have been under threat due to a disease called (COVID-19), which was first reported in China. Many methodical approaches have been reported to quantify chloroquine and hydroxychloroquine in blood, urine, plasma, serum, and pharmaceutical dosage form. Some of these techniques are spectrophotometry, liquid chromatography with a mass detector, gas chromatography, and ultra-performance, high-performance liquid chromatography (HPLC), in addition to electrochemical methods. This literature review discusses various analytical methods for the determining hydroxychloroquine and chloroquine.

Keywords: Review, Hydroxychloroquine, Chloroquine, Analytical Methods.

1.Introduction

Almost all types of human malaria have been commonly treated with Chloroquine (CQ) and Hydroxychloroquine (HCQ) **(Figure1**) [1]. Nevertheless, these medicines have been used to treat many diseases like hepatic amoebiasis, rheumatoid arthritis, and lupus erythematosus [2]. Since 1934 a chloroquine was first prescribed for the treatment of malaria; later, in 1955, hydroxychloroquine was introduced and became favored because of its safety profile [3]. Hydroxychloroquine has been considered as prospective as an active

remedy toward COVID 19 [4]. CQ is manufactured as tablets (administered orally) as its phosphate 500 mg for each tablet, while HCQ is manufactured as its sulfate with an oral dose of 200 mg [5]. In this literature review, various analytical methods are demonstrated for the quantitative determination of chloroquine and hydroxychloroquine; some of these techniques are reported, and it is given in **Table 1**.

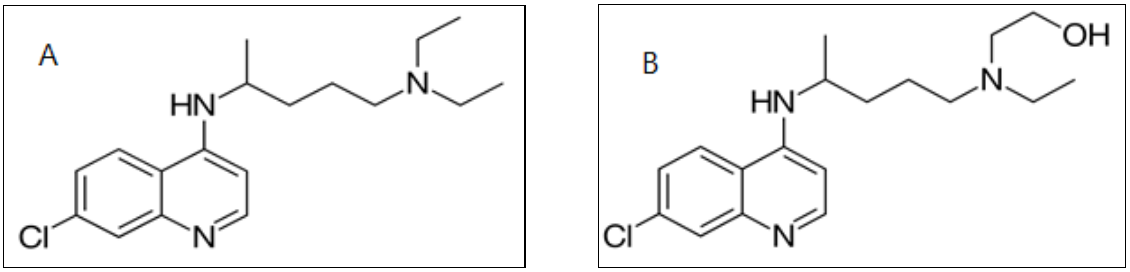

Figure 1: Chemical structure of A) Chloroquine, B) Hydroxychloroquine

Table 1: Some analytical methods for the determination of chloroquine and hydroxychloroquine**.**

Drug	Methods	sample	Results	Ref. No.
Chloroquine	high-performance liquid chromatography	plasma and urine	λ max = 254 and 340nm. linearity equle to (10 nmol.L^{-1}) for uv detection), (0.5 nmol.L^{-1} for fluorescence detection), RSD = 12%, r^2= 0.974-0.996.	[6]
Chloroquine	Photometric, ion-pair extraction	urine	λ max = 410 nm. linearity up to 120 mg.l^{-1}	[7]
Chloroquine	High performance thin layer chromatographic	biological fluids	LOD = 0.01 m.mol.L^{-1}, extraction efficiency = 76 ±7% , silica gel plates, using toluene/diethylamine (9:1)	[8]
Chloroquine	Column liquid chromatography	human plasma, red blood cells, Urine and Blood	mobile phase of phosphate buffer (pH 3.0)-acetonitrile (88:120) λ_{max} = 340 nm, %Recovery =75%	[9]
Chloroquine	High performance thin layer chromatographic	urine	Silica-gel of 60 plates (10X10)cm had impregnated fluorophore LOD = 0.25 micrograms.mL^{-1}, Rf = 0.27	[10]
Chloroquine	Colorimetric and thin-layer chromatographic methods	urine	concentrations up to (32 mug.ml^{-1}) LOD for modification I 0.3 mug.ml^{-1}, while that for modification II is 1 mug.ml^{-1}	[11]
Chloroquine	colorimetric methods	urine	linear range up to 8 micrograms/ml. LOD =1µ.ml^{-1}. LOD for its metabolites = 2 µ/ml	[12]
Chloroquine	High-performance liquid chromatography	biological fluids	Excit. wavelength 325nm, emi. wavelength 375 nm, mobile phase contains a mixture of acetonitrile with methanol-25% and ammonia (92.7:7.5, v/v) LOD = 5ng.mL^{-1}	[13]
Chloroquine	"reversed-phase ion-pair high-performance liquid chromatographic"	biological fluids	λ max = 254, mobile phase water - acetonitrile - methanol (78:28:4) plus 0.5M ammonium formate with 0.075M perchloric acid. nm, LOQ = 6ng.mL^{-1}	[14]
Chloroquine and Hydroxychloroquine	High-performance liquid chromatography	Serum and Blood	Excit. wavelength, 215 nm. LOQ for CQ =(0.005-0.01)mg.L^{-1}. LOQ for HOQ= 0.05 mg.L^{-1},	[15]

			sulfophenylpropyl -modified silica column, volumes (50-200 micro)	
Chloroquine	liquid chromatographic method	biological fluids	Linearity (0-200) $ng.mL^{-1}$ (for plasma), (0- 3) $ng.m^{-1}$ (for urine), r^2=0.990, CV= 4.8% in plasma and 4.4% in urine.	[16]
Chloroquine	Flow injection fluorimetric method	plasma	Laser λ at 355 nm, "linearity = (25-600) $\mu g.L^{-1}$", r^2 = 0.999, RSD = 4.3%	[17]
Chloroquine	High-performance liquid chromatography	Blood	For children Concentrations between 17 and 100 $nmol.L^{-1}$ (25%), 100 to 499 $nmol.L^{1-}$ (14%) and 500 $nmol.L^{-1}$ (13%) in Young age>	[18]
Chloroquine	laser-induced photochemical reaction and fluorescence	Plasma	λ_{max} =355nm using pulsed Nd:YAG laser Linearity = (25-600) $\mu g.^{L-1}$, r^2= 0.997, LOD=8$\mu g.L^{-1}$, RSD =4.3%, intrinsic fluorescence = 7 times.	[17]
Chloroquine	High-performance liquid chromatography	biological samples	λ max = 333nm, used, C(18) column, mobile phase (methanol phosphate) buffer pH 3 and perchloric acid (v/v) (250: 747.5 : 2.5)	[19]
Chloroquine	High-performance liquid chromatography with fluorescence detection	pharmaceuticals and biological fluids	Excitation wavelength 230 nm, emission wavelength 375 nm, linearity up to 0.5 ng/microL,Kromasil, C18, 5 microm column, mobile phase methanol -acetonitrile-ammonium acetate, (45:15:40). Re.+ (90.7-105.4)%	[20]
Hydroxychloroquine	differential pulse voltammetry and spectrophotometric	pharmaceutical formulations	Electrochemical, LOD = 11.2µg/mL, RSD = 0.46%, spectrophotometric, λ max = 343nm, LOD = 0.1$\mu g.mL^{-1}$, RSD = 0.36%	[21]
Chloroquine	High-performance liquid chromatography	plasma	Linearity (0-1000) ng/ml, r^2=0.9987, extracted with n-hexane, 10 microl aqueous layer	[22]
Chloroquine	capillary-LC with native laser	serum	(He-Cd 325 nm) detector, micro HPLC-LIF injection volumes were 200. separation time 3 min, LOD = 1.9, Re. more than 95% accuracy <10%	[23]
Chloroquine	reverse-phase liquid chromatography	dried blood spots	λ_{max} = 254nm, linearity (150 – 2500), solid-phase extraction is C18 Bond Elut cartridge) LOQ=50 $ng.mL^{-1}$, Cv =10.3%	[24]
Chloroquine	refractometry and colorimetry	pharmaceutical formulations	λ max = 528nm linearity (10 – 30)µL, r^2=0.946, Accuracy 92-103%, Precision (7-20)%	[25]
Chloroquine	charge–transfer formation	pharmaceutical formulations	λ_{max} = 520nm, Linearity=0.8-5 $mg.100mL^{-1}$ r^2=0.998.	[26]
Chloroquine	ion pair extraction	pharmaceutical formulations and urine	λ max = 420nm, Linearity=1.25-8.75 µg.mL-1 €= $4.09x10^4$.mol-1.cm-1, r^2=0.9989, RSD = 0.27	[27]
Chloroquine	High-performance liquid chromatography	"whole blood and finger-prick	λ_{max} =256nm, mobile phase (v:v:v) "diethylamine, acetonitrile and	[28]

		capillary blood"	methanol" (20:55:25,), LOQ =(25-50) ng.mL^{-1}, r = 0.997. Re. (74-87)%	
Chloroquine	Ion association complex	pharmaceutical formulations	1- λ_{max} =950nm, Linearity =(50-250) µg.mL^{-1} €= 1.79 × 10^{4}L.mol^{-1}.cm^{-1}, r^2 = 0.9992. LOD and LOQ equals (0.27 and 0.82) µg.mL-1 respectively. λ_{max} = 420nm, Linearity = (50-250) µg.mL^{-1}, € = 3.09 × 10^4 L.mol^{-1}.cm^{-1}, r^2 = 0.9996, LOD and LOQ = 0.15 and 0.460 µg.mL^{-1} respectively.	[29]
Chloroquine	High-performance liquid chromatography	plasma	λ_{max} =331nm, Linearity = (20-2000) nM, BDS-Hypersil (C18) 5m, 250×4.6)mm column, Mean Re. = 83.7%, r^2 =0.993	[30]
Chloroquine	oxidation of the drug with Fe(III)-1, 10 phenanthroline	pharmaceutical formulations	λ_{max} = 510nm, Linearity=20-320 µg.mL^{-1}, €= 666.66L.mol^{-1}.cm^{-1}, r^2 = 0.999, LOD equle 0.1915 µg.mL^{-1} while LOQ equle 0.5801 µg.mL^{-1}	[31]
Chloroquine		pharmaceutical formulations	λ_{max} = 285 and 345nm, Linearity= 50-250 µg/ml. r^2=0.999,	[32]
Hydroxychloroquine	Uv. spectrophotometric	Raw and pharmaceuticals	λ_{max} = 343nm, Linearity=1-20 µg.mL^{-1} €=0.2269x10^{3}L.mol^{-1}.cm^{-1}, r^2=0.9992\RSD= 0.169%.	[33]
Chloroquine	Uv spectral Method using 0.1N HCL	pharmaceutical formulations	λ_{max} = 342nm, Linearity=2.5-25 µg.mL^{-1}, €= 8.88x10^{3}L.mol^{-1}.cm^{-1}, LOD and LOQ equles 0.39 and 1.18 µg.mL^{-1} respectivly.	[34]
Chloroquine	HPLC method with diode array detector	whole blood and plasma	λ_{max} =343nm, Linearity= 10-5000 ng/mL (150 × 4.6) mm and 5µm (SB - CN) column, "mobile phase contain phosphate buffer" (pH 2.6) - acetonitrile 88:12, (v/v), LOD, LOQ = (10 and 4) ng.mL^{-1} Respectively.	[35]
Chloroquine	Ion pair reactions	pharmaceutical formulations	λ_{max} =420nm, Linearity=1-20 µg.mL^{-1} €= 1.79 × 10^{4}L.mol^{-1}.cm^{-1}, r^2=0.9992. LOD =, LOQ = 0.27 and 0.82 µg.mL^{-1} respectively, λ_{max}= 420nm, Linearity = 0.5 -12 µg.mL^{-1}, €=3.09 ×10^{4}L.mol^{-1}.cm^{-1}, r^2=0.9996, LOQ = 0.46 µg.mL^{-1} and LOD = 0.15 µg.mL^{-1}.	[36]
Chloroquine	Uv spectral Method using H_2O	pharmaceutical formulations	λ_{max} = 343nm, Linearity=10.88-30.56µg.mL^{-1}, r^2=0.99972.	[37]
Chloroquine	liquid chromatography	Blood	UPLC- HSS T_3, 2.5 µmand (75 mm x 2.1 mm) column, LOQ = 20 ng.ml^{-1}, precision (-12.1 to +11.1%), sensitivity. (1.4 to 15.0%), r =0.97,	[38]
Hydroxychloroquine	liquid chromatography with tandem mass spectrometry	mouse blood and tissues	λ_{max} =420nm, average Linearity = (1–2000) ng/mL, Thermo Aquasil C18 (50 × 4.6 mm, 3µ) column, mobile phase 0.20 % formic acid in methanol, r^2= 0.998. LOQ = 1.0	[39]

			ng.mL^{-1}.	
Chloroquine	LC-MS/MS	whole blood, plasma and dried blood spots	λ_{max} =420nm, average Linearity= (1.41–1552)ng.ml^{-1}, Sb-Cn 3.5 µm (50× 4.6) mm, mobile phase contain "acetonitrile + ammonium formate" 20 mM and formic acid (1%) pH = 2.6 (15–85), (v/v).	[40]
Hydroxychloroquine sulfate	ultra-HPLC (U-HPLC) method	whole blood	Excitation wavelength 335 nm , emission wavelength 390 nm, Linearity = (125 to 4000) ng.mL^{-1}, U-HPLC RP18 column, mobile phase piperazine buffer, (at pH equle to 9.8) plus acetonitrile (68:32), LOQ = 10 ng/mL , accuracies = (7.90-7.85)%, imprecisions (1.14 -8.78)%	[41]
Hydroxychloroquine	High-performance liquid chromatography	Blood	Excit. Wavelength = 337 nm , emi. Wavelengths = 405 nm, Linearity = (3-3000) ng/mL, column (C18), "mobile phase sodium phosphate (20 mM) buffer solution with 0.25% triethylamine and acetonitrile (60:40, v/v)", precisions=(1.3 to 7.3.).	[42]
Hydroxychloroquine	High-performance liquid chromatography	pharmaceutical formulations	Linearity = (0.200–6.004) µg mL^{-1}, LOD and LOQ = 0.066 µg mL^{-1}and 0.200 µg mL^{-1} respectively, RSD%= (98.25±1.05), r^2= 0.9999.	[43]
Hydroxychloroquine	High-performance liquid chromatography	pharmaceutical formulations	λ_{max} =254nm Linearity =(25-300) µg ml-1, "Zorbax C8, 250 mm × 4.6 mm i.d., column", RSD <1.5%, R^2 > 0.999	[44]
Hydroxychloroquine	LC-MS/MS method	plasma	Linearity = (2-1000) ng/mL, "Column (2.0 × 50) mm and 3 µm. For detection ESI, MRM are used". Ion pairs m/z equle to (336.1→247.1), Re. = (88.9-94.4)%.	[45]
Chloroquine and Hydroxychloroquine	two-dimensional isotope-dilution liquid chromatography-tandem mass spectrometry	serum	Injection volume of 5 µL, accuracy ≤ 9.59 %, imprecision ≤ 11.1 % for all quality controls.	[46]
Hydroxychloroquine	multisensing probe	pharmaceutical formulations	λ_{max} = 521, 600, 620 and 670 nm, LOD = 2.61nM for optical, 0.15nM fluorescence, and 0.85 nM electrochemical method.	[47]
Hydroxychloroquine	liquid phase microextraction-gas chromatography-mass spectrometry	urine, serum and saliva	LOD = 0.74 µg/kg, LOQ = 2.4 µg.kg-1 Re.= 93.9%-101.7% for serum, 95.2%-105.0%, for urine, 93.1%-102.3% for saliva.	[48]

2.Conclusions

The literature of different quantitative analytical methods for estimatig Chloroquine CQ and Hydroxychloroquine HCQ in their pharmaceutical preparations was carefully reviewed. Common instrumental methods for the determination of these drugs were Spectrophotometry, high-performance liquid chromatography HPLC with mass spectrometry

or diode array detector DAD, gas- chromatography, as well as electrochemical approaches. Chromatographic methods, especially HPLC, were the most routine practice. HPLC proved to be sensitive and accurate since it usually overcomes the errors that arise from interferences in the bulk of the pharmaceutical formulation.

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