IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, January 2024

A Detailed Examination of Atovaquone's Attributes and Analytical Approaches – An Effective Antimalarial Medication

Timir Kanta Padhan[1] and Dr. Alok Upadhyay[2]
Research Scholar, Department of Pharmacy[1]
Professor, Department of Pharmacy[2]
Sunrise University, Alwar, Rajasthan, India

Abstract: *The most incurable illness in the world is malaria, which is caused by many plasmosium species, including P. falciparum and P. vivax. The many drugs used to treat malaria included antifolate compounds such as pyrimethamine, proguanil, trimethoprim, and atovaquone; and aminoalcohol mixtures such as quinine, quinidine, chloroquine, and mefloquine. The most effective medication for treating malaria is atovaquone. It must be used alone or in combination with other antimalarial medications. Atovaquone is determined using a plethora of techniques, such as Liquid Chromatography-Mass Spectroscopy UV-Visible spectroscopy, and High Performance Liquid Chromatography. Pharmaceutical items are analysed using a variety of analytical techniques, all of which have been verified in compliance with ICH requirements. Therefore, the routine quality control analysis of atovaquone using this approach may be performed without risk.*

Keywords: Malaria, Antimalarial drugs, Atovaquone.

I. INTRODUCTION

Plasmodium parasites cause malaria, an ailment spread by mosquitoes. Malaria patients often have symptoms similar to the flu. Severe occurrences of the illness may progress to neurological abnormalities, unconsciousness, and even death. Usually ten to fifteen days after being bitten by a contaminated mosquito, symptoms appear. Malaria is prevalent in tropical and subtropical regions, where it kills around a million people annually.

Plasmodium, a kind of malaria parasite, belongs in the Phylum Apicomplexa. P. falciparum, P. malariae, P. ovale, P. vivax, and P. knowlesi are the parasites that cause malaria in humans.

P. falciparum is the most well-known species among the contaminated, standing out at over 75%, followed by P. vivax at around 20%. While P. falciparum malaria often accounts for the majority of fatalities, recent research suggests that P. vivax malaria is associated with potentially dangerous circumstances almost as frequently as P. falciparum infection. P. vivax is becoming less common outside of Africa. A few plasmodium species from higher gorillas have been linked to human contamination; however, they are not the same as P. knowlesi, a zoonotic animal variety that causes malaria in macaques. Male mosquitoes do not spread the disease; only female mosquitoes feed on plant nectar. It was about dusk when female anopheles mosquitoes went to breed. They often begin their search for dinner at dusk and continue until they are successful. Blood transfusions may also spread malaria parasites, albeit this is not very frequent.

The WHO survey report from 2018 states that 93% of malaria cases occurred in Africa, 3.4% in East Asia, and 2.4% in the Eastern Mediterranean region. P. falciparum was shown to be the primary cause of malaria in the African Region (99.7% of reported cases in 2018), as well as in a significant percentage of the WHO South-east Asia Region, the WHO Eastern Mediterranean Region, the WHO Western Pacific Region, and the WHO South East Asia Region.

Just 31 countries, where malaria is still endemic, had a significant fall in case frequency between 2015 and 2018 and were on pace to achieve a 40% or greater reduction in incidence by 2020. The Global Specialised Procedure for Malaria 2016–2030 targets for horrible in 2025 and 2030 cannot be met without accelerated transformation.

Resistance to antimalarial drugs is a hot subject these days. In endemic areas, the emergence of resistance to chloroquine has coincided with a sharp rise in malaria cases. Chromosome mutation resulted in P. falciparum malaria

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, January 2024

that is resistant to chloroquine. The intraerythrocytic tropozoite's digestive vacule's chloroquine collection changes when there is a chloroquine blockage. Multiple mutations in PfCRT, a protein that functions as a transporter in the parasite's digestive vacuole membrane, cause chloroquine resistance. significant resistance to chloroquine in both young children. Research into chloroquine resistance and subsequent treatments is desperately needed.

Pharmaceutical formulations and medicines in bulk are analysed both qualitatively and quantitatively using analytical methods. The methods have been highly helpful in both the past and the present. High Performance Liquid Chromatography UV-visible spectroscopy, mass spectrometry, and hyphenated methods such as GC-MS, LC-MS, and LC-NMR are among the most widely used analytical techniques. We have covered many atovaquone bulk analytical methods and formulations in this study.

Malaria life cycle

After a bite, mosquito salivary gland sporozoites swiftly enter the bloodstream and pass via open-response instances in hepatocytes, where they transform, develop, and take the shape of tissue schizonts. Depending on the plasmodium species, this basic asymptomatic tissue stage of infection lasts for 5 to 15 days. Following their split, tissue schizonts release hundreds of merozoites into the bloodstream, where they assault erythrocytes and initiate the erythrocytic cycle.

No kind of parasite remains in the liver when the tissue schizonts in P. falciparum and P. malariae infections rupture. However, tissue parasites in P. vivax and P. ovale infections persist and may cause erythrocytic contamination to relapse months or years after the first attack. As plasmodia cannot re-invade the liver once they reach the erythrocytic cycle, there is no tissue phase of contamination for jungle fever reduced by transfusion. Most parasites undergo agamic improvement in erythrocytes, progressing from juvenile ring formations to trophozoites and finally developing into schizonts. Erythrocytes harbouring schizonts rupture, releasing six to thirty-two merozoites, depending on the kind of plasmodium. This process is what causes clinical attacks that are feverish. More erythrocytes are attacked by the merozoites to advance the cycle, which lasts until the host dies or is adjusted by medication or acquired midway insusceptibility. The design of schizogony of an age of erythrocytic parasites determines the periodicity of parasitemia and feverish clinical symptoms. This process takes around 48 hours to complete for P. falciparum, P. vivax, and P. ovale, and about 72 hours for P. malariae.

When combined with proguanil, atovaquone, a highly lipophillic hydroxy napthaquinone or homologue of ubiquinone, is used to treat and prevent chloroquine-resistant P. falciparum. Because other anti-malarial medications have terrible side effects and drug resistance, atovaquine is a very effective anti-malarial medication that is essential to managing the condition.

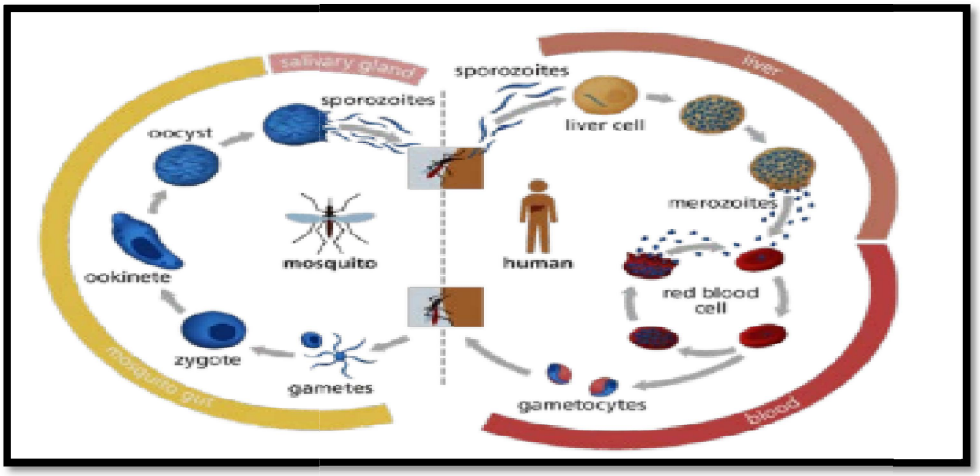

Figure 1: Life cycle of malaria

Malaria is treated with antimalarial medications. The goal of therapy is to cure symptoms such as fever, chills, and sweating that are caused by plasmodia release into the bloodstream, as well as to avoid death from severe malaria sickness. Every antimalarial medication has a unique mechanism of action for treating malaria. Both the erythrocytic and pre-erythocytic stages of development are active for some. A few medications are used to prevent malaria. The

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, January 2024

medications that work against P. falciparum also work against other human-affecting malaria species. The targeted tactics continue to develop P. falciparum resistance and fast-acting blood schizontocidal antimalarial medications globally.

Table 1: Various classes of antimalarial drugs

Class	Drugs
4-Amino quinolines	Chloroquinine, Amodiaquine, Piperaquine
Quinoline methanol	Mefloquine
Cinchona Alkaloid	Quinine, Quinidine
Biguanides	Proguanil, Chloroproguanil
Diamino Pyrimidine	Pyrimethamine
8-Amino quinoline	Primaquine, Bulaquine
Sulfonamide and Sulfones	Sulfadoxine, Dapsone
Tetracycline	Doxycycline
Sesquiterpene lactones	Artesunate, Artemether, Arteether
Amino alcohols	Halofantrine, Lumefantrine
Mannich base	Pyronaridine
Napthaquinone	Atovaquone

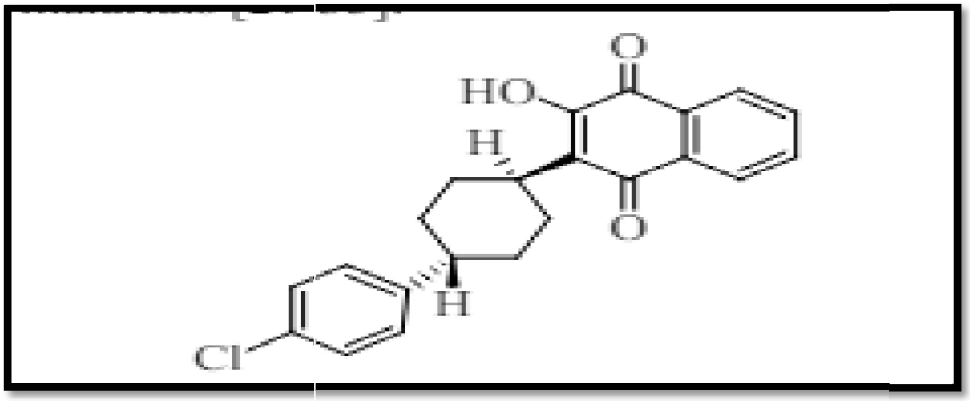

Figure 2: Chemical structure of atovaquone

IUPAC name	2-hydroxy-3-{(1R,4R)-4-(4-chlorophenyl) cyclohexyl}-1,4-dihydronapthalene-1,4-dione
Molecular formula	C22H19ClO3
Solubility	Ethanol, Methanol, slightly soluble in water
LogP	5.9
Half life	2.2 -3.2 days
Molecular weight	366.8 g/mol
Melting point	216–219 ℃

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, January 2024

Mechanism of action

Ubiquinol is competitively inhibited by atovaquone. It causes loss of mitochondrial function by blocking the electron transport chain in the mitochondria at the BC1 complex.Atovaquone inhibits the electron transport chain in the mitochondria, especially at the cytochrome bc1 complex. Dihydro-orotate dehydrogenase plays a crucial role in the parasite's ability to provide orotate for pyrimidine in the mitochondria during the intraerythrocytic phase of infection. Atropaquone's inhibition of the BC1 complex affects the concentration of metabolites in the pathway leading to the production of pyrimidines.

Absorption: Atovaquone has a limited bioavailability that is significantly influenced by food and formulation. When the suspension is taken with dinner, its bioavailability doubles. Around 47% of the medication is bioavailable when taken with meals. The bioavailability is 23 percent without food.

Volume of distribution: 0.60± 0.17 L/kg.

Protein binding: 99% plasma proteins.

Excretion: The half-life of atovaquone is long becouse of enterohepatic cycling and fecal disposal. There was no excretion of atovaquine via urine.

UV methods for Atovaquone

Varsha HC created a very simple and accurate UV-visible spectroscopic technique, which was verified for the measurement of atovaquone in both its pure form and its nano suspension. The Varian Cary C50 was the instrument utilised for spectrophotometric measurements. Atovaquone was measured in pH 8 at 494 nm. It was discovered that there was linearity in the concentration range of 20–140 µg/ml. The created procedure was then verified in accordance with ICH regulations.

A method for atovaquone was developed by Srujani C et al. utilising the hydrotropic solubilization approach. The hydrotropic solubilization approach is used to medications that are not sufficiently soluble in water. Hydrotropic solvents, such as sodium benzoate, urea, salicylate, and piperazine, are used in varying quantities. Throughout the whole procedure, the Shimadzu UV-1800 spectrophotometer with UV-probe software was used. To increase atovaquone's water solubility, 1M piperazine was used. The estimated wavelength is 274 nm. There was observed to be linearity between 4 and 20 µg/ml. It was discovered that the average percent label claim for atovaquone tablets was 98.75%. In compliance with ICH principles, the suggested approach was verified.

A straightforward and accurate technique for estimating atovaquone in bulk and tablet formulations was developed by Kalpesh NP et al. Using methanol as the solvent, the wavelength was determined to be 251 nm. Within the range of 1 to 10 µg/ml was the linearity. The approach was used to investigate the marketed formulation of atovaquone and was validated in accordance with ICH criteria. The 99.14±1.14% label claim ± standard deviation was supported. This meticulous approach was used for both the formulation of atovaquone and routine examination of medicines in bulk.

HPLC methods for Atovaquone

A straightforward and accurate RP-HPLC technique for the simultaneous measurement of proguanil and atovaquone in pharmaceutical dosage form was developed by Lakshmana Rao A et al. Chromatographic separation was performed using a Kromasil C18 column with a 1 ml/min flow rate and a 50:50 mobile phase of 0.1% OPA:ACN with UV detection at 287 nm. The duration of retention for k was 2.15 and 2.48 minutes, respectively. In compliance with ICH requirements, the devised approach was validated. The method's linearity was excellent between 25 and 150 µg/ml for proguanil and 6.25 and 375 µg/ml for atovaquone. Proguanil and atovaquone had a percent mean recovery that ranged from 98.86 to 99.97%. This technique works well for both tablet formulation and routine atovaquone analysis in bulk.

A accurate and quick RP-HPLC technique was established by Naazneen S. and Sridevi A. for the measurement of atovaquone and proguanil in tablet formulations. Gradient HPLC was used to perform the technique using a C18 column (250mm × 4.6 mm, 5µ). The mobile phase consisted of 90:10 v/v acetonitrile-methanol in a 30:70 v/v ratio and 10 mM ammonium formate at pH 3.5. The effluent was measured at 254 nm, and the flow rate was 0.9 ml/min. Proguanil and atovaquone had retention times of 3.8 and 7.3 minutes, respectively. Method validation followed ICH norms. For proguanil, the linearity was from 2.5 µg/ml to 20 µg/ml, while for atovaquone, it was 6.25 µg/ml to 50 µg/ml. Proguanil's percent recovery ranged from 98.38 to 101.09%, whereas the other drug's range was 98.62 to 100.99%. This technique was developed for routine examination and was also used to study the forced deterioration of tablet formulations.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, January 2024

A straightforward and accurate HPLC technique was developed by Viplava K and Haritha PV to determine the presence of atovaquone in bulk medications. According to ICH criteria, atovaquone was found to deteriorate under various circumstances. The degradants that resulted from this degradation, together with atovaquone, were separated using Thermo Hypersil BDS C18, 250mm×4.6mm×5µm columns with buffer:acetonitrile as the mobile phase. The wavelength was 283 nm, and the flow rate was 1.5 ml/min. A retention time of 4.9 minutes was observed. The method was accepted in compliance with ICH regulations. The method is used to the analysis of atovaquone in the deteriorated materials created under various stress conditions.

Hyphenated techniques for atovaquone

Using lapachol as an internal standard, Sanjay G. et al. devised the LC-APCI technique, which describes how to determine atovaquone in human plasma. Atovaquone's plasma was extracted using a single-step precipitation process, resulting in a mean recovery of 94.17% without sacrificing linearity or sensitivity. For atovaquone and lapachol, a warmed nebuliser in negative various reaction observation mode was used, with transitions of m/z 365.2 → m/z 337.1 and m/z 240.9 → m/z 185.7. Chromatographic separation using 100 µL of plasma extraction on a Synergi 4 µm Polar-RP 80A column. 10 µL of injection was used, and the assay ran in one minute. The developed analytical technique may be used successfully in pharmacokinetic investigations on atovaquone suspension controlled in healthy individuals or those living with HIV.

An analytical assessment of a UPLC-MS/MS approach for atovaquone quantification in plasma was developed by Allison BC et al. For the assessment of atovaquone in plasma to support preclinical and clinical preliminary work, the approach that was shown was sufficiently delicate. The technique utilised to analyse atovaquone in plasma samples is UPLC-MS/MS. Atovaquone was used to precipitate proteins, and the medication was recovered from 25µL K2-EDTA. On a 2.5µm Polar-RP100 A column synergi, the test solution was separated. Using an electrospray ionisation source, atovaquone and its internal standard were found on an API 4000 mass analyser over a period of 1.3 minutes. The Food and Drug Administration approved the method's validation. Both of the calibration curves, which run from 250–5000 ng/ml and 5000–50,000 ng/ml, were derived using the pharmacokinetic parameters. QC levels were produced for low mid and high concentrations for both lower and higher concentration ranges. The accuracy and precision were established at ≤9.1% and ≤±9.4%. Results from the study of the matrix, dilution, and stability effects were within acceptable bounds.

II. CONCLUSION

In conclusion, atovaquone is a new derivative of napthaquinone that has several therapeutic uses and is a common ingredient in antimalarial formulations. Atovaquone was routinely identified and quantified using the analytical techniques previously mentioned.

REFERENCES

[1]. Bruce-Chwatt LJ. Malaria and its control: present situation and future prospects. Annu Rev Public Health 8, 75-110. (1987).

[2]. Sahu M, Tediosi F, Noor AM, Aponte JJ, Fink G. Health systems and global progress towards malaria elimination, 2000-2016. Malar. J.,19, 1-2 (2020).

[3]. World Health Organization. World Malaria Report 2015 - Summary, 2015.

[4]. Tangena JA, Hendriks CMJ, Devine M, Tammaro M, Trett AE, Williams I, DePina AJ, Sisay A, Herizo R, Kafy HT, Chizema E, Were A, Rozier J, Coleman M, Moyes CL. Indoor residual spraying for malaria control in sub-Saharan Africa 1997 to 2017: an adjusted retrospective analysis. Malar. J. 19, 150. (2020).

[5]. Wellems TE, Plowe CV. Chloroquine-resistant malaria. J. Infect. Dis. 184, 770-6. (2001).

[6]. Le Bras J, Durand R. The mechanisms of resistance to antimalarial drugs in Plasmodium falciparum. Fundam. Clin. Pharmacol., 17, 147-153 (2003).

[7]. Fidock DA, Nomura T, Talley AK, Cooper RA, Dzekunov SM, Ferdig MT, Ursos LMB, Bir Singh Sidhu A, Naudé B, Deitsch KW, Su XZ, Wootton JC, Roepe PD, Wellems TE. Mutations in the P. falciparum digestive vacuole transmembrane protein PfCRT and evidence for their role in chloroquine resistance. Mol. Cell, 6, 861-871 (2000).

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, January 2024

[8]. Wongsrichanalai C, Pickard AL, Wernsdorfer WH, Meshnick SR. Epidemiology of drug-resistant malaria. Lancet Infect Dis 2, 209-18. (2002).

[9]. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, Lampah DA, Price RN. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med. 5, e128. (2008).

[10]. Ringwald P. Current antimalarial drugs: Resistance and new strategies. Bull. Acad. Natl. Med., 191, 1273-1284 (2007).

[11]. Chishimba S, Kobayashi T, Mulenga M, Phiri M, Mharakurwa S, Thuma P, Moss WJ. The impact of insecticide-treated nets on acquired humoral immunity to plasmodium falciparum. Am. J. Trop. Med. Hyg.,83, 361 (2010).

[12]. Pouniotis DS, Proudfoot O, Minigo G, Hanley JL, Plebanski M. Malaria parasite interactions with the human host. J Postgrad Med 50, 30-4. (2004).

[13]. Newbold CI. Antigenic variation in Plasmodium falciparum: mechanisms and consequences. Curr. Opin. Microbiol. 2, 420-5. (1999).

[14]. Sinnis P. The malaria sporozoite's journey into the liver. Infect Agents Dis. 5, 182-189 (1996)

[15]. https://www.yourgenome.org/facts/what-is-malaria . Accessed 15 june, 2020. image credit: Genome Research Limited.

[16]. Tripathi K. Essential of Medical Pharmacology (7th Edition). (2013).

[17]. Dutta GP. New antimalarial drug discovery in India and future strategy for malaria control. Proc. Indian Natl. Sci. Acad., 1, 82 (2016).

[18]. Mokhtari RB, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. oncotarget., 8, 38022 (2017).

[19]. Chattopadhyay R, Mahajan B, Kumar S. Assessment of safety of the major antimalarial drugs. Expert opinion on drug safety., 6, 505-521 2007.

[20]. Dhanawat M, Das N, Nagarwal R, Shrivastava S. Antimalarial Drug Development: Past to Present Scenario. Mini-Reviews Med. Chem., 9, 1447-1469 (2009).