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ASSESSMENT OF PHARMACEUTICAL QUALITY PARAMETERS OF ATOVAQUONE ORAL SUSPENSION

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1.ABSTRACT

Malaria is a life-threatening vector-borne parasitic disease caused by protozoa of the genus *Plasmodium* and remains a major public health problem in tropical and subtropical regions. Among the five species infecting humans, *Plasmodium falciparum* is the most pathogenic and responsible for the majority of malaria-related deaths. The disease is transmitted through the bite of infected female *Anopheles* mosquitoes and presents with symptoms such as fever, chills, headache, fatigue, anemia, and severe complications including cerebral malaria and jaundice. The pathophysiology of malaria involves destruction of red blood cells, cytokine release, cytoadherence, and microvascular obstruction. Antimalarial therapy plays an essential role in the prevention and treatment of malaria. Atovaquone, a hydroxynaphthoquinone antiprotozoal agent, acts by inhibiting the mitochondrial electron transport chain of the parasite, thereby interfering with pyrimidine synthesis and DNA replication. The present article focuses on the preformulation, formulation, and evaluation of Atovaquone oral suspension. Preformulation studies included organoleptic properties, solubility, pKa, pH, partition coefficient, melting point determination, FTIR compatibility studies, UV spectrophotometric analysis, and stability studies. The formulation of suspension involved the use of excipients such as poloxamer 188, phospholipon 90H, glycerin, and purified water to improve stability and dispersibility. The prepared suspension was evaluated for sedimentation volume, viscosity, particle size, drug release, redispersibility, and zeta potential. The study highlights the importance of optimized formulation strategies in improving the stability, dissolution, and bioavailability of Atovaquone oral suspension for effective antimalarial therapy.

2.KEYWORDS: Malaria; *Plasmodium falciparum*; Antimalarial agents; Atovaquone; Oral suspension; Preformulation studies; Suspension formulation; FTIR; Drug release; Particle size analysis; Zeta potential; Stability studies; Bioavailability; Protozoal infection; *Anopheles* mosquito.

3.INTRODUCTION

It is an endemic vector-borne parasitic disease caused by protozoan parasites of the genus Plasmodium in tropical and subtropical regions worldwide. Plasmodium consists of over 200 species, infecting mammals, birds, and reptiles, and malaria parasites generally tend to be host-specific. Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium knowlesi are the five known species of the genus Plasmodium that causes malaria in humans.

Among them, P. falciparum is the most pathogenic species that accounts for 60–70% deaths. Malaria parasite completes its life cycle in two different hosts; invertebrate-Anopheles mosquitoes, and vertebrate-humans.[1]

SYMPTOMS

The most common early symptoms of malaria are fever, headache and chills.Symptoms usually start within 10–15 days of getting bitten by an infected mosquito.Symptoms may be mild for some people, especially for those who have had a malaria infection before. Some types of malaria can cause severe illness and death. Infants, children under 5 years, pregnant women, travellers and people with HIV or AIDS are at higher risk. Severe symptoms include:

extreme tiredness and fatigue

impaired consciousness

multiple convulsions

difficulty breathing

dark or bloody urine

jaundice (yellowing of the eyes and skin)

abnormal bleeding.[2]

ETIOLOGY

Protozoan parasites of the genus Plasmodium originate from photosynthetic protozoa named Dinoflagellates. About 200 different species of protozoa have been identified so far and among them, at least 13 species are known to be pathogenic to humans. Five of the

parasites namely P. falciparum, P. vivax, P. malariae, P. ovale (P. ovale curtisi and P. ovale wallikeri), and P. knowlesi are well-known etiologies of malaria in humans.

In Africa, the most prevalent and pathogenic species is P. falciparum. However, malaria infection from most malaria-endemic regions of Africa shows the presence of multiple sympatric species and co-infection within an individual human host or mosquito vector. P. malariae is the species most commonly found in sympatry with P. falciparum in malaria-endemic regions of Africa.

In each endemic area, malaria is transmitted by a specific set of Anopheles species. So far, more than 400 different species of Anopheles mosquitoes have been identified. But only 30 of them are known to transmit malaria. All vectors of malaria undergo the bite between dusk and dawn.

Stability is observed in the distribution pattern of the mosquito species in malaria-endemic regions of the African continent. The complete disappearance of a given vector species from a region is unusual and when the non-indigenous vector is introduced to the area, it is a serious public health concern since it is known to result in devastating epidemics. Indigenous vectors are hard to eradicate with known vector eradication activities.[3]

LIFE CYCLE OF MALARIA

The life cycle of the malaria parasite is a complex process involving an Anopheles mosquito and a vertebrate host. The first stage of the infection is the entrance of the sporozoites in mosquito saliva into the skin and bloodstream of the human host and then, it invades hepatocytes to undergo asexual replication. During this phase (hepatic or pre-erythrocytic phase) the rupture of infected hepatocytes results in the release of thousands of merozoites. In the case of P. vivax and P. ovale infections, some form dormant hypnozoites which remain within hepatocytes for periods of several months, and even as long as 4 years, before developing and multiplying to initiate a new episode of erythrocytic infection.

The erythrocytic infection involves the interaction of the merozoites with the red blood cells (RBC). The merozoites head orients and adjoin with the erythrocytes membrane by deforming the surface host cell. Then, through parasite-induced reorganization of the erythrocyte cytoskeleton, the parasite enters the erythrocyte to undergo the second asexual reproduction. While younger erythrocytes are targeted favorably by P. vivax and P. ovale, erythrocytes of any age are invaded by P. falciparum and P. knowlesi. In contrast, P. malariae prefers senescent erythrocytes. After invading RBC, merozoites reproduce into

trophozoites and then into schizonts which erupt from the erythrocytes to release merozoites and reinvade new RBCs and continue the asexual replication cycle.

The sexual reproduction cycle of malaria starts when a portion of trophozoites matures to male and female sexual progeny or gametocytes. The transmission of the malaria parasite from the mammalian host to the mosquito is mediated by these gametocytes. During the bite of an anopheles mosquito, the matured gametocytes will be taken to the midgut of the mosquito. Inside the midgut, gametocytes get converted into fertile gametes and the next stage involves the conversion of zygotes into ookinetes which are motile and invasive. The ookinetes in turn get converted into oocysts in the midgut basal lamina. The oocyst then matures releasing sporozoites, which migrate to the salivary gland of the mosquito. The parasite is transmitted to another mammalian host through an infected mosquito bite.

PATHOPHYSIOLOGY OF MALARIA

Malaria pathophysiology differs between uncomplicated and severe disease. In uncomplicated malaria, fever results from the rupture of infected red blood cells and the release of merozoites, which stimulate macrophages to produce pro-inflammatory cytokines, especially TNF-α. The fever pattern varies by species: Plasmodium vivax and Plasmodium ovale cause tertian fever (every 48 hours), Plasmodium malariae causes quartan fever (every 72 hours), while Plasmodium falciparum typically produces an irregular fever pattern. Severe malaria is mainly due to cytoadherence, where infected red blood cells bind to vascular endothelium. In P. falciparum, the virulence factor PfEMP1 forms surface “knobs” that mediate adhesion to endothelial receptors, leading to sequestration of infected cells in deep microvasculature. This process contributes to complications such as cerebral malaria. In addition, rosetting (binding of infected to uninfected red blood cells) impairs microcirculation and causes tissue hypoxia. Parasite toxins such as glycosylphosphatidylinositol (GPI) further stimulate excessive cytokine production, resulting in high fever, endothelial activation, nitric oxide release, tissue damage, and suppression of bone marrow function.[4]

ANTI-MALARIAL AGENTS

Antimalarial medications are a type of antiparasitic chemical agent, often naturally derived, that can be used to treat or prevent malaria.Effective anti-malarial drug treatment reduces malaria transmission. This alone can reduce the incidence and prevalence of malaria, although the effects are greater in areas of low transmission where a greater proportion of the infectious reservoir is symptomatic and receives anti-malarial treatment.[5]

CLASSIFICATION

a. Cinchona Alkaloids:

e.g. Quinine, quinidine

b. 4-Aminoquinolines:

e.g. Chloroquine, amodiaquine.piperaquine

c. 8-Aminoquinolines:

e.g. Primaquine, Pamaquine

d. Quinoline-Methanol:

e.g. Mefloquine

e. Naphthaquinone:

e.g. Atovaqoune

f. Pyrimidines:

e.g. Pyrimithamine, Trimethoprim

g. Sulphones:

e.g. Dapsone, Sulfamethopyrazine

h. Biguanides:

e.g. Proguanil, Chloroproguanil

i. Sesquiterpine Lactone:

e.g. Artemisinin, Artemether

k. Antibiotics:

e.g. Tetracycline, doxycycline, clindamycin.

ATOVAQOUNE

Atovaquone medication used in the prevention and treatment *Pneumocystis jirovecii* pneumonia (PCP), and malaria (in combination with proguanil), as well as for treatment of babesiosis (in combination with azithromycin).

Atovaquone is an analogue of ubiquinone (coenzyme Q10) and exerts its pharmaceutical effects by binding to the ubiquinone binding site on the parasitic mitochondrial cytochrome bc1 complex, thus inhibiting a step of protozoal pyrimidine synthesis.

Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of both ubiquinone and lawsone.

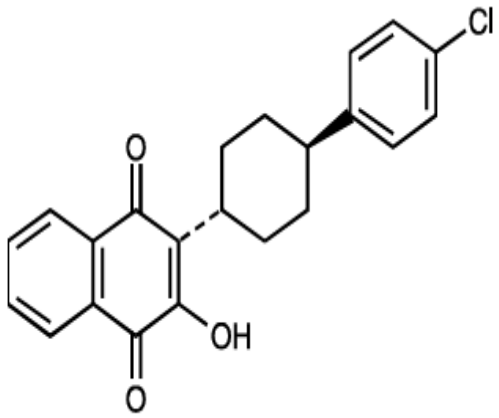
Molecular weight:366.84

Molecular formula: C22H19ClO3

MECHANISM OF ACTION

Atovaquone selectively inhibits the malarial cytochrome bc_1 complex in the parasitic electron transport_chain, collapsing the mitochondrial membrane potential. The malarial electron transport chain does not contribute significantly to ATP synthesis; thus, it is believed that parasite death is due to the indirect inhibition of dihydroorotate dehydrogenase, which requires transport chain function and is essential to pyrimidine biosynthesis – a process required for DNA replication. [10]

Proguanil, via its metabolite cycloguanil, functions as a dihydrofolate reductase inhibitor, halting parasitic deoxy thymidylate synthesis.[6]



4.METHODS AND MATERIALS

PREFORMULATION STUDIES

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.[7]

*Various preformulation studies include:

1. **PHYSICOCHEMICAL PROPERTIES**

a) Organoleptic properties
b) Solubility
c) pKa
d) P^H
e) Partition coefficient
f) Melting point

2. **COMPACTABILITY STUDIES**

a) FTIR-Spectrophotometer

3. OPTICAL PROPERTIES

a) Determination of λ-max

PHYSICOCHEMICAL PROPERTIES

a) Organoleptic properties

i)Appearance: Transferred approximately 2 gm of the sample on a white paper spreaded uniformly and examined visually.

ii)Color: A small quantity of pure drug powder was taken in a butter paper and viewed in well illuminated place.

Table 1: organoleptic properties.

Properties	Description
Color	Yellow color
Odor	Odorless
Taste	Bitter
Texture	Crystalline powder

b) Solubility: soluble in chloroform, sparingly soluble in acetone and Dimethyl sulfoxide, slightly soluble in octanol, ethyl acetate and polyethylene glycol 200, very slightly soluble in 0.1N sodium hydroxide, insoluble in water.

C) pKa

Weigh a small amount of Atovaquone and dissolve it in ethanol and distilled water**.**

Calibrate the pH meter using standard buffer solutions.

Place the solution on a magnetic stirrer**.**

Add 0.1 N NaOH slowly from a burette.

Record the pH after each addition of NaOH.

Draw a graph of pH vs volume of NaOH added.

The pH at half-neutralization point is the pKa value**.**

d) pH

*Weigh a small amount of Atovaquone.

*Dissolve it in a suitable solvent such as distilled water or buffer solution to prepare a dilute solution.

*Calibrate the P^H meter using standard buffer solutions (pH 4, 7, and 9).

*Immerse the P^H electrod**e** into the drug solution.

e) Partition coefficient

Procedure:

25 mg of Atovaquone with aqueous phase and n-octanol was taken in three separating funnels. The separating funnels were shaken for 2 hours in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase spectrophotometrically.

g) Melting point

Melting point of Atovaquone was determined by Open capillary method.[8]

COMPATIBILITY STUDY

Fourier transform infrared spectroscopy was employed to characterize the possible interactions between the Atovaquone and carriers.

Drug – Excipient Interaction Studies by FTIR: - Infra-red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm-1 in a FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.[9]

OPTICAL PROPERTIES

Determination of λ max

A solution of Atovaquone containing the concentration 10 µg/ ml was prepared in 0.1 N HCL and UV spectrum was taken using double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm. [10]

PHARMACOKINETIC PROPERTIES OF ATOVAQUONE

- **Absorption:** Atovaquone is poorly absorbed from the GI tract, but absorption increases significantly when taken with fatty food.
- **Peak Plasma Concentration:** Reached within 1–8 h after oral administration.
- **Distribution:** Atovaquone is highly protein bound (>99%) and widely distributed in body tissues.
- **Metabolism:** Atovaquone undergoes minimal metabolism in the body.
- **Elimination Half-life:** Approximately 2–3 days due to enterohepatic recycling.

- **Excretion:** Mainly excreted unchanged in feces, with minimal urinary excretion.[11]

FORMULATION OF SUSPENSION

The pharmaceutical suspension is a biphasic liquid or semi-solid dosage form where the finely divided insoluble solid drug particles are homogeneously dispersed in a liquid or semi-solid medium. The insoluble solid drug particles act as the dispersed phase or internal phase.

ADVANTAGES

Improve the chemical stability of some drugs.

Higher bioavailability than other dosage forms. Order of bioavailability: Solutions>suspension>capsules> compression tablets > coated tablets.

Duration and onset of action can be controlled.

Mask the unpleasant taste of the drug.

DISADVANTAGES

Physical stability, sedimentation and compaction can causes problems.

It is bulky sufficient care must be taken during handling and transport.

It is difficult to formulate

METHOD OF PREPARATION OF SUSPENSION

- Dispense the raw materials as per formula or batch manufacturing record (BMR) and sieve them.
- Place the portion of solvent, solid sweetener, buffer, surfactants, humectants, and other water-soluble excipients into a stainless-steel vessel and mix to dissolve.
- Add the liquid sweetener, API and other liquid excipients, and a portion of solvent into a stainless-steel vessel and mix.
- Mix the suspending agents into a portion of the solvent.
- Dissolve the preservatives and antioxidants into a portion of the solvent.
- Mix the coloring agents and flavoring agents into a portion of the solvent.
- Mix and homogenize all the above steps.
- Check the parameters such as description, weight per ml, pH, and viscosity of the sample of bulk product.

INGREDIENTS

Atovaquone oral suspension contains 750 mg of atovaquone per 5 mL and the following non-medicinal ingredients:

benzyl alcohol, citric acid, hypromellose, poloxamer 188, purified water, saccharin sodium, sodium citrate dihydrate, flavour (tutti frutti) and xanthan gum. Tutti frutti flavour contains artificial flavours, benzyl alcohol, dl-alpha-tocopherol, maltodextrin and propylene glycol.

FORMULATION OF ATOVAQUONE SUSPENSION

Drug concentration: 15% atovaquone (API).

Key excipients:

- Poloxamer 188 (2%) → wetting agent, improves dispersibility.
- Phospholipon 90H (1%) → stabilizer, prevents aggregation.
- Glycerin (10%) → viscosity enhancer and suspending agent.
- Purified water (q.s.) → vehicle.

Processing steps (top-down method):

1. Wet milling (trituration).
2. Probe sonication.
3. Microfluidization (high-pressure homogenization)

Formulation of micronized suspension of atovaquone was optimized by employing a 32 full factorial design keeping poloxamer 188 (wetting agent) and phospholipon 90H (stabilizer) as the influential variables affecting the dependent variables viz.

particle size and polydispersity index (PdI). Selected formulations from the optimized design space were further evaluated for dissolution and the formulation exhibiting maximum dissolution within 120 min was selected.

The optimized batch consisting of atovaquone (15%), poloxamer 188 (2%), phospholipon 90H (1%), glycerin (10%) in the aqueous vehicle was microfluidized.

EQUIPMENTS

- Beaker
- Measuring cylinder
- Glass rod
- Mortar and pestle
- Magnetic stirrer

- Mechanical stirrer
- Homogenizer
- pH meter
- Weighing balance
- Sieve
- Funnel
- Spatula
- Sonicator
- Viscometer
- Bottle/container for storage. [13]

5.EVALUATION OF SUSPENSION

a) Sedimentation volume:

Sedimentation volume (F) is a ratio of the final volume of sediment (Vu) to the original volume of sediment (Vo) before settling. 50ml of each suspension were transferred to 50 ml measuring cylinders and the volume of sediment formed was noted at every 24 hr for 7 days. The sedimentation volume F (%), was calculated using the formula: F = 100 Vu/ Vo

b) Viscosity measurement:

The viscosity of the samples was determined at 25oC using the Brookfield Synchro lectic viscometer, model LVF (Brookfield Laboratories, Massachusetts) at 30 revolution/min.

c) Particle size measurement:

The particle size in the prepared suspensions was measured by optical microscopy using a trinocular microscope at 100x (10×10) magnification. The size of 100 particles were measured and the average particle size of was determined.

d) Drug release:

The release studies were carried out at 37± 0.5oC by using a beaker method rotating cellophane membrane apparatus. A 1000 ml volume of the 0.1N HCL of the release media. The cellophane membrane containing 5.00 ml of solution or a suspension of the suspension salt was placed inside the vessel at time zero. Release of the drug salt from the cellophane membrane into the aqueous sink condition studied from the following type of test preparation;

(i) a solution of the salt,

(ii) salt suspensions,

(iii) suspensions formed in situ in cellophane membrane cell. Salt solutions were obtained from dissolving in 0.1 N HCL. After 15 min taking 5 ml solution was withdrawn and maintained sink condition. Samples were withdrawn after time interval 30, 45, 60, 75, 90, 105, 120 and135 min. Maintaining sink condition, the taking solutions were further diluted with 0.1 N HCL and absorbance measured in double beam UV spectrophotometer

e) Re dispersibility

- Number of inversions required to re disperse sediment
- Good suspension should re disperse easily

f) Particle Size Analysis

- Determined by microscopy or dynamic light scattering
- Smaller particle size improves dissolution and bioavailability
- Atovaquone nanosuspensions typically show particle size <500 nm

g) Zeta Potential

- Indicates physical stability
- Value > ±20 mV suggests good stability
- Prevents aggregation of particles.[14]

STABILITY STUDIES

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparation.

TYPES OF STABILITY STUDIES ON DRUG SUBSTANCES

A comprehensive pharmacopoeial protocol (USP) prescribes the criteria for acceptable levels of physical, chemical, microbiological, therapeutic and toxicological stability studies.

✓ Physical stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

✓ Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

✓ Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product.

✓ Therapeutic stability

The therapeutic effect (Drug Action) remains unchanged.

✓ Toxicological stability

Toxicological stability has no significant increase in the toxicity occurs.

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. In the early stages, the stability testing is performed by the accelerated stability studies which mainly are performed at high temperature\ humidity.

TYPES OF STABILITY TESTING

□Long-Time stability testing - 25oC/60% RH or 30oC/65%RH for 12 months

□Intermediate stability Testing – 30±2oC and 65±5% RH for 6 months

□Accelerated Stability Testing - 40oC/75% RH for 6 months.[15]

PACKAGING, STORAGE REQUIREMENTS AND LABELLING OF PHARMACEUTICAL SUSPENSIONS

Pharmaceutical suspensions for oral use are generally packed in wide-mouth containers with adequate space above the liquid to allow proper mixing before use. Parenteral suspensions are usually packed in glass ampoules or vials.[16]

Ideal Requirements of Packaging Material

An ideal packaging material for suspensions should possess the following characteristics:

- It should be inert and non-reactive with the formulation.
- It should protect the product from light, air, moisture, and microbial contamination throughout its shelf life.
- It should be economical and easy to manufacture.

- It should ensure convenient delivery and handling of the product.

Materials Used for Packaging

Glass Containers

Glass is commonly used for packaging pharmaceutical suspensions. The major types include:

- Soda-lime glass
- Borosilicate glass

Amber-colored glass containers are preferred for light-sensitive formulations because they prevent the passage of ultraviolet (UV) light. Amber color can be produced by adding specific additives during glass manufacture.

Disadvantages of Glass

- Fragile and easily breakable
- Heavy compared to plastic containers
- Possibility of extraction of glass constituents into the product

Plastic Containers

Due to the disadvantages of glass, plastics are increasingly used for both sterile and non-sterile suspensions.

Advantages of Plastic

- Non-breakable
- Lightweight
- Flexible
- Easy to transport and handle

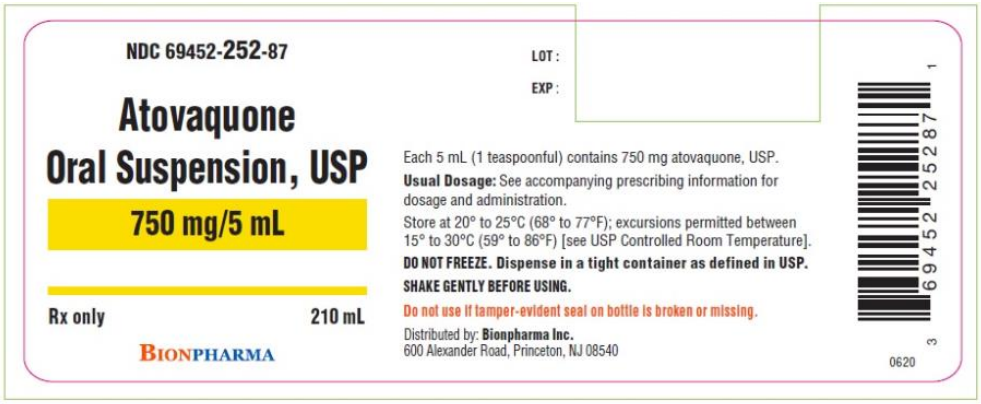
Common Plastic Materials

- Polyethylene
- Polyvinyl chloride (PVC)
- Polystyrene
- Polycarbonate.[16]

Important Labelling Instructions

- Shake well before use
- Do not freeze
- Protect from direct light (for light-sensitive drugs)

- For dry suspensions, specify the quantity of vehicle to be added before reconstitution



Storage Conditions

- Suspensions should be stored in a cool place.
- Refrigeration should generally be avoided unless specifically recommended.
- Freezing must be avoided because it may cause aggregation of suspended particles.
- Recommended storage temperature: 20–25°C.[17]

6.RESULT AND DISCUSSION

Preformulation studies confirmed the suitability of Atovaquone for oral suspension formulation. FTIR studies showed no interaction between the drug and excipients. The optimized suspension exhibited good physical stability, satisfactory viscosity, easy redispersibility, and uniform particle size distribution. Drug release studies demonstrated improved dissolution due to particle size reduction by microfluidization and sonication. Stability studies indicated that the formulation remained stable under recommended storage conditions without significant changes in appearance, pH, or drug release profile.

7.CONCLUSION

The present study successfully formulated and evaluated a stable Atovaquone oral suspension for antimalarial therapy. Preformulation studies provided essential information regarding the physicochemical and compatibility characteristics of the drug. The optimized suspension formulation demonstrated satisfactory physical stability, improved drug dissolution, good redispersibility, and acceptable viscosity. The use of wet milling, sonication, and microfluidization effectively reduced particle size and enhanced the bioavailability of Atovaquone. Overall, the formulated oral suspension may serve as an effective and patient-friendly dosage form for the treatment and prevention of malaria.

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