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(RESEARCH ARTICLE)

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Development and estimation of an oro-dispersible anti-malarial dosage form for pediatric patient

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Abstract

Artemether-Lumefantrine tablets are inconvenient for caregivers to administer as they need to be crushed and mixed with water or food for infants and young children. Further, in common with other anti-malarial, they have a bitter taste, which may result in children spitting the medicine out and not receiving the full therapeutic dose. There was a clear unmet medical need for a formulation of AL specifically designed for children.

Keywords: Oro-dispersible; Pediatric; Artemisinin; Lumefantrine; Malaria

1. Introduction

Infants and children, the most vulnerable to malaria with over 1,700 deaths per day from malaria in this group. However, until there were few WHO – endorsed pediatric anti –malarial formulation available. Half world population is at risk of malaria and an estimated 243 million case occurred in 2008. Of these, there was an estimated 863,000 million death, 767,000 of which occurred in Africa where malaria is the leading cause of mortality in children under 5 years. (WHO 2004a; WHO 2009a). However the World Malaria Report, 2018 indicate, an estimate cases of malaria occurred worldwide (95% confidence interval [CI]:206 -258 million), compared with 251 million case in 2010 (95% CI: 231-278 million) and 231 million case in 2017 (95% CI; 211-259 million).Children aged under 5 year are the most vulnerable group affected by malaria.

1.1. Malarial definition

Malaria is caused die the protozoan parasite Plasmodium Human malaria is caused by four different species of Plasmodium: *P. falciparum, P. malaria, P. oval and P. vive.*

1.2. Malarial life cycle

The life cycle of Plasmodium falciparum begins with the bite of an infected female mosquito. The mosquito while taking a blood meal, releases sporozoites into the blood stream which invade the liver cells within 30 minutes of the release. Inside the hepatic cells of the liver, the parasites rapidly differentiate and undergo asexual multiplication resulting in the release of merozoites which invade other liver cells. These merozoites from the hepatocytes burst into the host's blood stream where they invade the erythrocytes. Further multiplication takes place inside the erythrocytes enlarging into ring trophozoites which divide asexually producing schizonts. The schizonts divide further causing a release of merozoites when the erythrocytes are ruptured. The released merozoites in the blood stream are responsible for the clinical manifestation in malaria illness such as fever, joint and muscle pains and chills. This stage called the erythrocytic stage is the asexual life cycle of the parasite and usually lasts for 48hours. Some of the schizonts divide into sexual forms resulting in male and female gametocytes. The gametocytes are taken up by the female anopheles mosquito during another blood meal from a host. The male gametocytes undergo a rapid nuclear division inside the midgut of the

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mosquito resulting to microgametes which fertilize the female microgametes producing ookinete. The ookinete later crosses the gut wall as oocyte which subsequently ruptures releasing merozoites into the body cavity of the mosquito from where they eventually migrate to the salivary gland of the mosquito. With another blood meal the mosquito transmits the merozoites into another victim and continues the life cycle.(Adapted from http://www.cdc.gov/malaria/about/biology/).

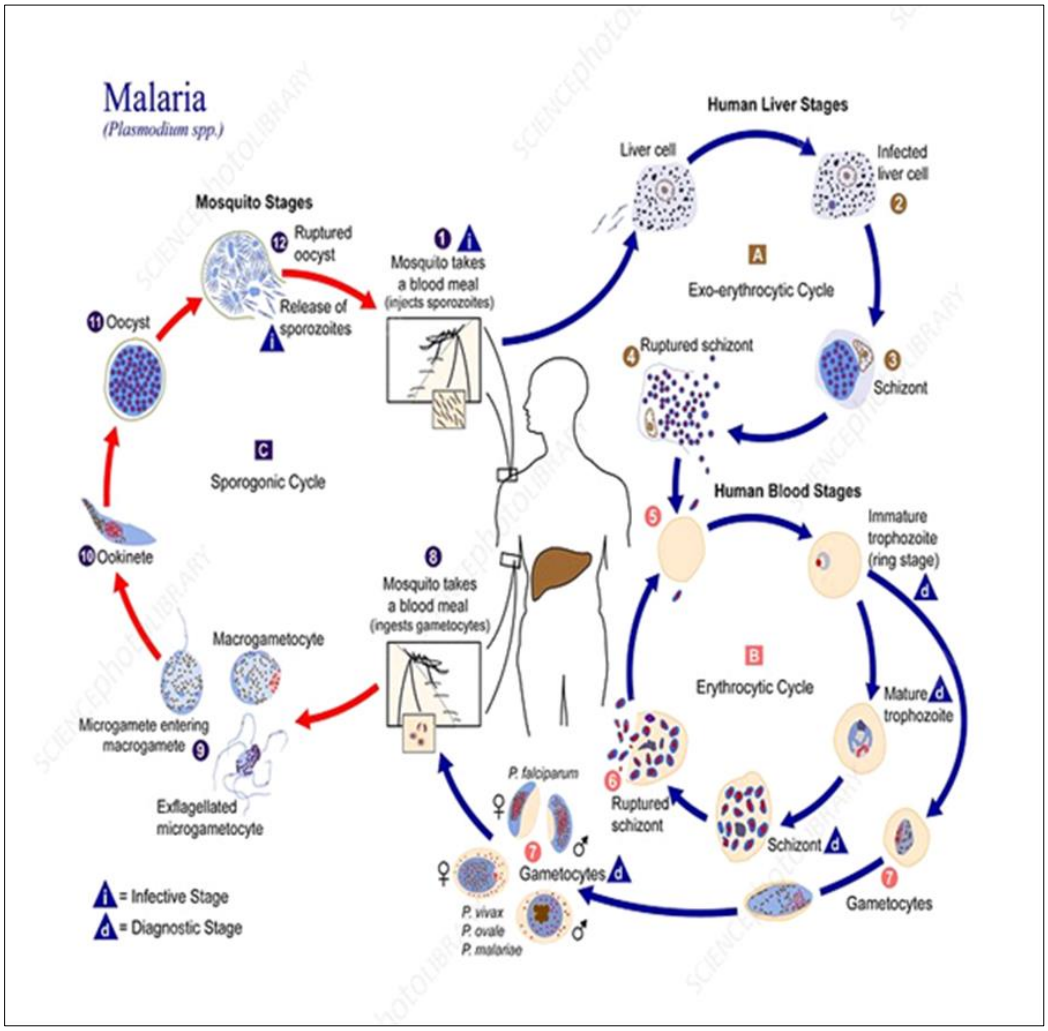

Figure 1 Antimalarial drugs target the erythrocytic stage of malaria infection

1.3. Malarial Symptoms

The most severe form is caused by Falciparum; the symptoms are fever, headache, chill, muscular aching and weakness, vomiting cough, Diarrhea and abdominal pain. The possibility of falciparum malaria is considered in all cases of unexplained fever starting at any time between 7 days after the possible exposure to malaria and 3 months after the last possible exposure. Any individual who experiences a fever in this interval should immediately seek diagnosis and effective treatment, and inform medical personnel of the possible exposure to malaria infection. Falciparum malaria may be fatal if treatment is delayed beyond 24 h after the onset of symptoms.

1.4. Malarial Treatment

Treatment of malaria with drugs is the most common and one of the most important measures for the control of malaria. The goals of treatment of uncomplicated malaria are: to provide rapid and long lasting cure, to reduce morbidity including malaria-related anemia, to prevent the progression of uncomplicated malaria to severe and potentially fatal diseases and to minimize the likelihood and rate of development of drug resistance in addition to reducing transmission.

Antimalarial drugs can be classified into related groups based on the chemical structure of the

Compounds as follows:

- 8-Amino quinolones (Mefloquine, primaquine)
- 4-Amino quinolones (Chloroquine, amodiaquine, piperaquine)
- Antifolates (Sulfonamides, sulfones)
- Aryl amino alcohols (Quinine, Lumefantrine, Halofantrine)
- Artemisinis (Artemisinin, Dihydroartemisinin, artesunate, artemether, arteether)
- Biguanides (proguanil and chlorproguanil)
- Unclassified quinolones (Pyronaridine)
- Antibiotics (tetracyclines, azithromycine)
- Naphthoquinones (Atovaquone)

They can also be classified based on their mode of action (Warhust, 2001a) as blood schizonticides, antifolates and antimitochondrials.

Antimalarial drugs are used for the treatment and prevention of malaria infection. Most antimalarial drugs target the erythrocytic stage of malaria infection, which is the phase of infection that causes symptomatic illness (figure 1). The extent of pre-erythrocytic (hepatic stage) activity for most antimalarial drugs is not well characterized.

Treatment of the acute blood stage infection is necessary for malaria caused by all malaria species. In addition, for infection due to Plasmodium ovale or Plasmodium vivax, terminal prophylaxis is required with a drug active against hypnozoites (which can remain dormant in the liver for months and, occasionally, years after the initial infection).

The mechanisms of action, resistance, and toxicities of antimalarial drugs will be reviewed here. Use of these agents for prevention and treatment of malaria is discussed in detail separately. (See "Prevention of malaria infection in travelers" and "Treatment of severe malaria" and "Treatment of uncomplicated falciparum malaria in nonpregnant adults and children".)

1.5. Artemisinin Derivatives

The artemisinin are derived from the leaves of the Chinese sweet wormwood plant, Artemisia annua. They have been used in China for the treatment of malaria for over 2000 years and came to attention outside of China in the 1970s and 1980s. Artemisinin formulations include artemether, arteether, dihydroartemisinin, and artesunate. They are marketed as part of combination therapy throughout the world.

Artemisinins appear to act by binding iron, breaking down peroxide bridges, leading to the generation of free radicals that damage parasite proteins. They act rapidly, killing blood stages of all Plasmodium species and reducing the parasite biomass. Artemisinins have the fastest parasite clearance times of any antimalarial. Artemisinins are active against gametocytes, the parasite form that is infectious to mosquitoes, and their use has been associated with reduced malaria transmission when they were introduced in Thailand.

1.6. History of Quinine

The discovery of quinine is considered the most serendipitous medical discovery of the 17th century [1] and malaria treatment with quinine marked the first successful use of a chemical compound to treat an infectious disease. Quinine, as a component of the bark of the cinchona (quina-quina) tree, was used to treat malaria from as early as the 1600s, when it was referred to as the "Jesuits' bark," "cardinal's bark," or "sacred bark." These names stem from its use in 1630 by Jesuit missionaries in South America, though a legend suggests earlier use by the native population. According to this legend, an Indian with a high fever was lost in an Andean jungle. Thirsty, he drank from a pool of stagnant water and found that it tasted bitter. Realizing that the water had been contaminated by the surrounding quina-quina trees he thought he was poisoned. Surprisingly, his fever soon abated, and he shared this accidental discovery with fellow villagers, who thereafter used extracts from the quinaquina bark to treat fever. The legend of quinine's discovery accepted in Europe differs though, and involves the Spanish Countess of Chinchon who, while in Peru, contracted a fever that was cured by the bark of a tree. Returning to Spain with the bark, she introduced quinine to Europe in 1638 and, in 1742, botanist Carl Linnaeus called the tree "Cinchona" in her honour.

Before 1820, the bark of the cinchona tree was first dried, ground to a fine powder, and then mixed into a liquid (commonly wine) before being drunk. In 1820, quinine was extracted from the bark, isolated and named by Pierre Joseph Pelletier and Joseph Caventou. Purified quinine then replaced the bark as the standard treatment for malaria. Quinine and other cinchona alkaloids including quinidine, cinchonine and cinchonidine are all effective against malaria.

The efficacies of these four alkaloids were evaluated in one of the earliest clinical trials, conducted from 1866 to 1868 in 3600 patients using prepared sulfates of the alkaloids. With the main outcome measure of "cessation of febrile paroxysms", all four alkaloids were found to be comparable, with cure rates of >98%. However, after 1890 quinine became the predominantly used alkaloid, mainly due to a change in supply from South American to Javan cinchona bark, which contained a higher proportion of quinine. Quinine remained the mainstay of malaria treatment until the 1920s, when more effective synthetic anti-malarials became available. The most important of these drugs was chloroquine, which was extensively used, especially beginning in the 1940s.

2. Material and methods

2.1. Material

Table 1 Material and Suppliers

S. No.	Material	Suppliers
1	Artemether	Mangalam drugs Pvt
2	Lumefantrine	Mangalam drugs Pvt
3	Hydroxyl propyl cellulose	Welming pharmaceuticals, India
4	Polysorbate 80	Welmingchemicals, India
5	Iso propyl alcohol	Loba chemie. Pvt ltd,. Mumbai
6	Microcrystalline cellulose	Welming chemicals, India
7	Croscarmelose sodium	S.D.Fine-Chemi.,Pvt Ltd., Mumbai
8	Aerosil	Amaratal & Co., Chennai
9	Magnesium stearate	Loba chemie., Pvt. Ltd., Mumbai

2.2. Methods

2.2.1. Evaluation of drug

- Description
- Melting point
- Solubility
- Water content by Loss on Drying
- Hygroscopic Nature

2.2.2. Differential scanning calorimetry – to analyse the incompatibility of the drug with the polymer

2.2.3. Physical evaluation of the granules

- Bulk Density
- Tapped density
- Carr's Index
- Haunser's Ratio
- Angle of Repose

2.2.4. Evaluation of the formulated tablet

- Friability
- Hardness
- Thickness
- Uniformity of weight
- Swelling and erosion study
- Assay
- *In vitro* drug release

- Stability Study
- Release kinetics

3. Results and discussion

Table 2 Organoleptic Properties of Drug

Organoleptic properties	Artemether	Lumefantrine
Colour	white crystals	yellowish powder
Odour	Odourless	Odourless
Taste	Slightly Bitter	Bitter
Microscopic examination	Crystalline powder	Amorphous powder

3.1. Solubility Studies

Table 3 Solubility Profile of Artemether

Sr. No.	Solvent	Solubility
1	Distilled water	Insoluble
2	PBS (pH 6.8)	Soluble
3	Acetonitrile	Soluble
4	0.1 N HCL	Soluble
5	Ethanol	Soluble
6	Dichloromethane	Soluble

Table 4 Solubility Profile of Lumefantrine

Sr. No.	Solvent	Solubility
1	Distilled water	Insoluble
2	PBS (pH 6.8)	Soluble
3	Acetonitrile	Soluble
4	0.1 N HCL	Soluble
5	Ethanol	Soluble
6	Dichloromethane	Soluble

3.2. Identification Of Drug

Identification of artemether and lumefantrine is carried out by Infra-Red Absorption Spectrophotometry.

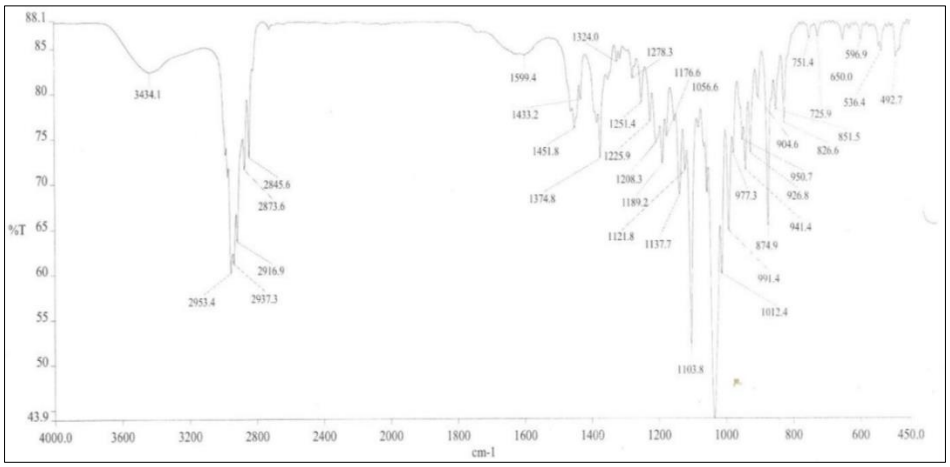

Figure 2 For Artemether

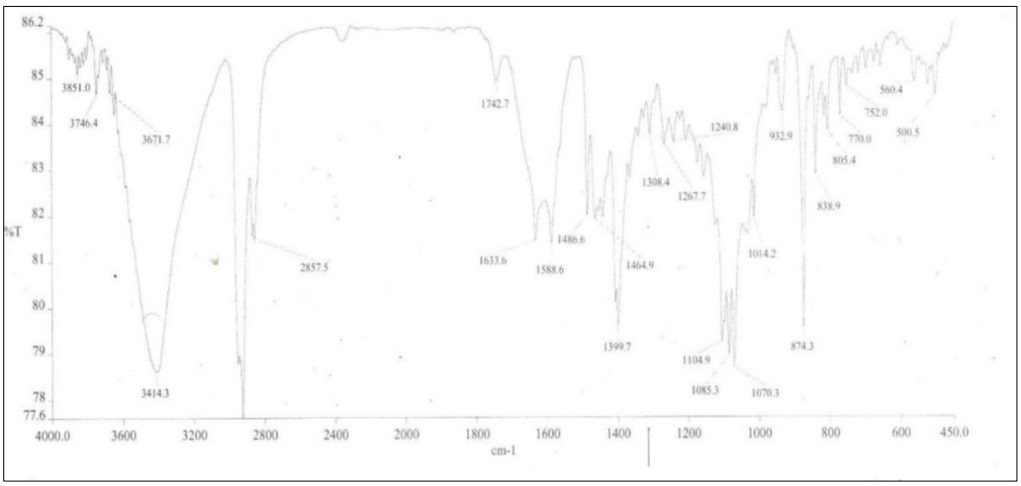

Figure 3 For Lumefantrine

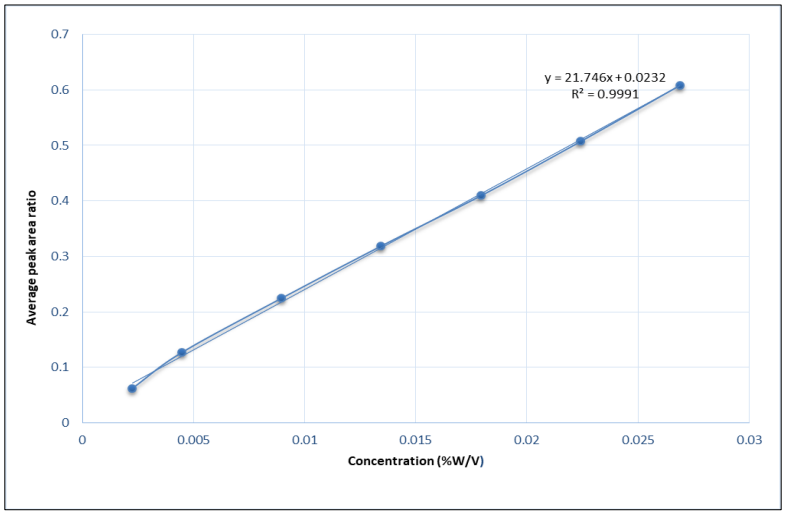

Figure 4 Calibration curve of Artemether:

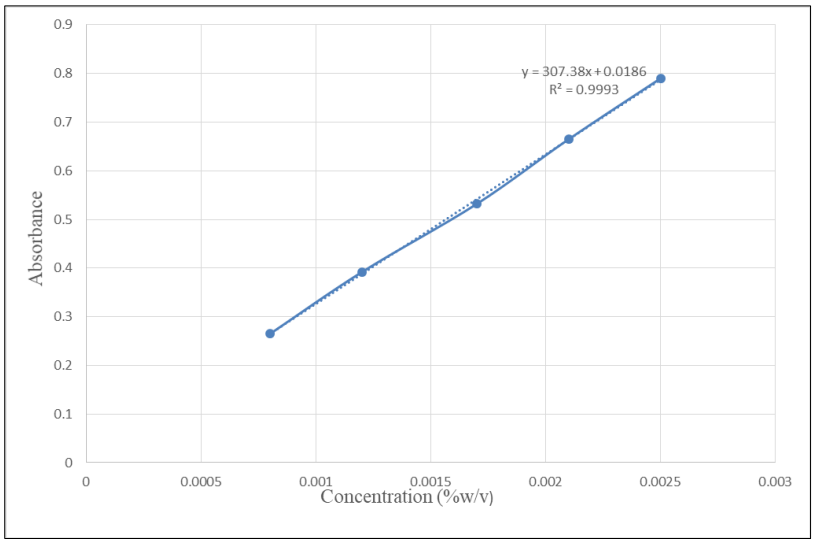

Figure 5 Calibration curve for lumefantrine in 0.1 M Methanolic HCL

Table 5 Stability study

Study	Storage Condition	Minimum time period covered by data at submission
Long term	25 ± 2 °C 60 ± 5 % RH or 30 ± 2 °C 65 ± 5 % RH	12 month
Intermediate	30 ± 2 °C 65 ± 5 %RH	6 month
Accelerated	40 ± 2 °C and 75 ± 5 % RH	6 month

4. Conclusion

Recent advances in oral drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance.

In the present research work an attempt was made to formulated oral dispersible tablets specially developed for pediatric using excipients of varying the concentration by wet granulation technique.

The API was subjected to Preformulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with API.

In the successful tablet formulation, the selected tablets were studied for their quality control test via Appearance, Thickness, Hardness, Weight variation, and Disintegration time and in- vitro dissolution study, and Assay.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest among all of us.

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