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STABLE ANTIMALARIAL COMBINED FORMULATION DEVELOPMENT FOR BITTER TASTING DRUGS

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ABSTRACT

Malaria is a major global health problem, particularly in developing countries in Africa, Asia, and Latin America. Here are some statistics on malaria worldwide, According to the World Health Organization (WHO), there were an estimated 229 million cases of malaria worldwide in 2019, with 94% of these cases occurring in sub-Saharan Africa. Malaria caused an estimated 409,000 deaths in 2019, with young children under the age of five and pregnant women being the most vulnerable groups. Children under the age of five are particularly vulnerable to malaria, accounting for approximately two-thirds of all malaria deaths worldwide. Malaria disproportionately affects people living in poverty, who may not have access to proper health care or preventative measures such as bed nets or insecticides. Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated malaria by the World Health Organization (WHO). ACTs are a combination of two or more drugs, one of which is an artemisinin derivative. Though for malarial treatment, ACTs must be taken as prescribed, and patients may be required to take multiple tablets over several days. Compliance can be a challenge, particularly in settings where patients may not have easy access to health care or may not understand the importance of completing the full course of treatment. Artemisinin-based combination therapies (ACTs) can have a bitter taste, particularly in their tablet form. This bitter taste is a common side effect of the medication and can be a challenge for some patients, particularly children, who may have difficulty swallowing the tablets or may refuse to take the medication altogether. To overcome this, Dry powder mix formulation was developed which conceals bitter taste and overcome stability of antimalarial drug. Through innovative manufacturing processes and the use of less expensive raw materials, we have created a dry powder mixing formulation that offers significant cost savings to patients and healthcare providers.

Keywords: Malaria, Global health problem, Developing countries, Artemisinin-based combination therapies (ACTs), Bitter taste and Dry powder mix formulation

1. INTRODUCTION

Dry powder formulations of antimalarial drugs are a type of formulation that can be reconstituted with a liquid (usually water) to form a suspension or solution for oral administration(1,2). These formulations are often used for paediatric patients or patients who have difficulty swallowing tablets or capsules. There are several advantages to using dry powder formulations for antimalarial drugs, including(3):

1. Dose accuracy: Dry powder formulations allow for precise dosing of medication, which is important in the treatment of malaria.(3)

2. Ease of administration: These formulations can be reconstituted with water or other liquids to create a suspension or solution that is easy to swallow, making it a good option for patients who have difficulty swallowing tablets or capsules.(3,4)
3. Stability: Dry powder formulations can be more stable than other types of formulations, such as liquid suspensions, which can be prone to degradation over time.(3,4)
4. Storage: Dry powder formulations are typically more stable at room temperature than liquid formulations, which may require refrigeration.(3,4)

Artemisinin-based combination therapies (ACTs) are the recommended treatment for uncomplicated Plasmodium falciparum malaria by the World Health Organization (WHO) and other health organizations.(5–8) This is because ACTs have been shown to be highly effective in treating malaria, reducing the number of parasites in the blood and curing the infection.(5,9)

There are several reasons why ACTs are the recommended treatment for malaria(5,9,10)

1. Resistance: Malaria parasites can develop resistance to antimalarial drugs, making them less effective. By using a combination of drugs with different mechanisms of action, the development of resistance is less likely.
2. Synergy: The drugs in an ACT work together to increase their effectiveness. Artemisinin-based drugs are fast-acting, rapidly reducing the number of parasites in the blood, while the partner drug has a longer half-life, ensuring that the parasites are completely eliminated.
3. Reduced transmission: By rapidly reducing the number of parasites in the blood, ACTs can reduce the likelihood of transmission of malaria to mosquitoes, thereby reducing the overall transmission of the disease.
4. Improved compliance: The use of a combination of drugs in a single pill can improve compliance, making it easier for patients to complete the full course of treatment and reducing the likelihood of drug resistance.
5. Overall, the use of ACTs is an important strategy in the fight against malaria, helping to ensure that patients receive effective treatment and reducing the likelihood of the development of drug resistance.

So, the main aim of the work was to formulate Paediatric Formulation Design, development and evaluation of Taste Masked Oral Dry Powder (ready for reconstitution) of antimalarial drugs for the effective management of Malaria(11,12). The research work is based upon the formulation development and evaluation of taste masked dry oral dosage form of anti-malarial drugs.(13) To Enhance stability of Antimalarial Drugs(14,15). To increase Patient compliance. To mask and improve the Taste of bitter tasting of drugs. To increase the solubility. To increase the bioavailability. To increase shelf life. Explore feasibility of combination therapy. This could be achieved by coating the drug with HPMC and HPβ-CD in different ratios. (15)

2. MATERIALS AND METHOD:

2.1.MATERIALS

Artemether (98.63% purity) and lumefantrine(98.69% purity) were obtained as a gift sample from Medley Pharmaceuticals Ltd. Methanol (solvent) was purchased from Vishal chemicals, Mumbai. All other chemicals and reagents used in the study were of the analytical grade and obtained from Vishal chemicals, Mumbai.

2.2.METHODS

2.2.1. PROCEDURE FOR TASTE MASKING OF DRUGS:

Artemether and Lumefantrine dry powder was prepared by Kneading method where Artemether and Lumefantrine with HPβ-CD and HPMC in different molar ratios (1:1, 1:5 and 1:10) were mixed in a mortar for about 60 minutes with constant trituration and then add 5 ml methanol and dry 60°C for 24hr.which are coated to form a dry powder. Following ratios were used for the preparation of formulation:

2.2.2. FORMULATION OF ARTEMETHER AND LUMEFANTRINE DRY POWDER READY FOR RECONSTITUTION

Table No. 1: Formulation of Artemether and Lumefantrine dry powder ready for reconstitution

Ingredients	B1 (1:1)	B2 (1:1:25)	B3(1:1.5)
Artemether	80mg	80mg	80mg
Lumefantrine	480mg	480mg	480mg
HPβ-CD	1560mg	1930mg	2330mg
HPMC	177mg	177mg	177mg

2.2.3. PROCEDURE FOR PREPARATION OF DRY POWDER READY FOR RECONSTITUTION

1. Taste Masked Artemether and Lumefantrine were passed through sieve #40
2. Transfer the shifted material to polybag and blend for 15 minutes.
3. Pass the remaining ingredients such as, Avicel CL.611, Xanthan gum, An. Citric acid,

Methyl paraben, Propyl paraben Pineapple flavour through sieve #40 and mix the ingredients with taste masked drugs in geometric proportion

3. Transfer all the materials to polybag and blend for 15 minutes.

Table No. 2: PREPARATION OF DRY POWDER READY FOR RECONSTITUTION

Ingredients	F1	F2	F3	F4
B3	3067	3067	3067	3067
Avicel	150	300	450	-
Anhydrous citric acid	15	15	15	15
Methyl paraben	10	10	10	10
Propyl paraben	1	1	1	1
Colloidal silicon	350	350	350	350
Xanthan gum	20	40	60	-
Pineapple flavor	87.6	87.6	87.6	87.6

4. CHARACTERIZATION OF FORMULATED DRY POWDER(16)

4.1.Determination of particle size(17):

a. Sieve analysis: The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom). Procedure: A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve number 20, 30, 40, 60, 80, and 100. 10 grams of drug was weighed accurately and transferred to sieve number 20 which were kept on top. The sieves were shaken for about 5-10 minutes on mechanical sieve shaker having bottom tap motion. Then the drug retained on each sieves was taken, weighed separately and amount retained was expressed in terms of percentage.

b. Angle of repose: The flow property was determined by measuring the Angle of Repose. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Values of q are rarely less than 20°, and values of up to 40° indicate reasonable flow potential. Above 50o, however, the powder flows only with difficulty if at all.

$$\theta = \text{Tan-1}\ (h/r)$$

where, h = height the pile.

r = radius of the pile. Angle of repose

5 grams of the sample was taken in a funnel fixed in a holder, 6 cm above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined using the above formula. This was repeated 3 times for a sample.

c. Determination of bulk density and tapped density: A quantity of 20 g of the powder (W) from each formula was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to keep in bulk density apparatus for tapping. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following Formulas:

$$\text{Bulk density } (\rho 0) = M/Vo$$

Where, M = mass of the powder

Vo = volume of the powder

$$\text{Tapped density } (\rho t) = M/Vf$$

Where, M = weight of sample powder taken Vf = tapped volume

d. Compressibility index (Carr's index): Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having value of less than 18 % is defined as the free flowing material.

$$CI = 100 (V0 - Vf) / V0$$

Where CI = Compressibility index

e. Hausner's Ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density.

3.1.2. LOSS ON DRYING: In pharmacy, the term loss on drying, commonly referred to as LOD, is an expression of moisture content on a wet- weight basis, which is calculated as

$$\% \text{ LOD} = \frac{\text{Weight of water in sample}}{\text{Weight of the sample}}$$

Method:

The moisture content of substances was determined gravimetrically on a SARTORIUS MA-45 moisture balance Approximately 1gm of sample was uniformly placed onto the sample pan and then the heating cycle was started. The percentage of moisture content was calculated from the weight loss of sample by heating. The instrument was allowed to cool between tests and triplicate test was run for each sample

3.2. CHARACTERIZATION OF RECONSTITUTED DRY SUSPENSION:(2,16)

3.2.1. SEDIMENTATION VOLUME(17,18)

The prepared dry suspension having weight 7.5g was dispersed in 20 ml of distilled water The suspension was kept for 5 hours and observed every hour to check for sedimentation From 1-3 hour the powder was well dispersed After 3 hour the powder became to settle and After 5 hours the powder in the suspension was completely settled.

Formula is F = Vu/Vo Where,

Vu- Ultimate Volume of Sediment

Vo- Initial Volume of Suspension

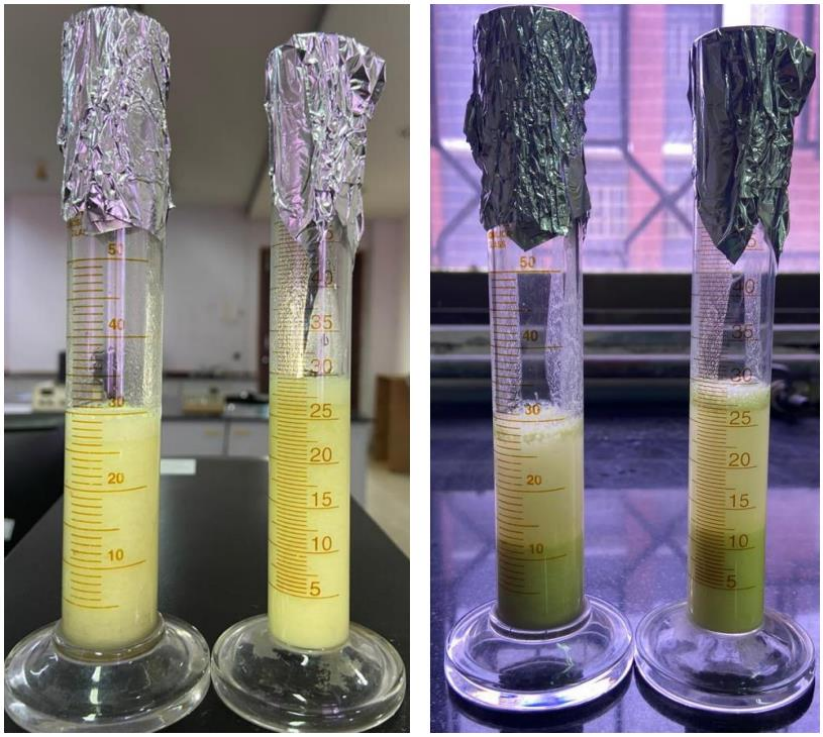

Fig. 1: Sedimentation volume

3.2.2. pH MEASUREMENT

The pH of the formulated dry suspension upon reconstitution was measured by Systronics Digital pH meter 3.35. Determination of pH pH of suspension was determined by using pH meter. pH of the phases of suspension also contributes to stability and characteristic of formulations. pH of the suspension was recorded from time to time.

Fig. 2: pH measurement

3.2.3. VISCOSITY

Viscosity of suspension is a great importance for stability and palatability of suspensions. Suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation.

Sedimentation is governed by stoke's law, $V = d2 (\rho s – \rho l) g / 18 n$

V - Terminal settling velocity

d –diameter of the settling particle

ρs – density of the settling solid (dispersed phase)

ρl - density of the liquid (dispersion medium)

g – Acceleration due to gravity

Ƞ – viscosity of dispersion medium when the viscosity of dispersion medium increases the settling velocity decreases.

3.2.4. DETERMINATION OF VISCOSITY

The measurement of viscosity of suspension was done with Brookfield viscometer (DV-E). 10ml of reconstituted suspension was taken in a vial/ 10ml beaker and spindle was dipped into the gel formulation, suspension was measured by rotating spindle number 64 at 12 rpm.

Fig. 3: Viscosity

3.2.5. DEGREE OF FLOCCULATION (β)

It is the ratio of the sedimentation volume of the flocculated suspension ,F , to the sedimentation volume of the deflocculated suspension, F∞.

Degree of flocculation(β):- $\frac{F}{\text{Foo}} = \frac{volume\ of\ flocculated\ suspension}{volume\ of\ deflocculated\ suspension}$

Degree of Flocculation The minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.

3.2.6. IN VITRO DISSOLUTION STUDY(19)

Dissolution profile of dry powder was determined using the USP (type I) basket apparatus with a speed of 50 rpm. Dissolution was tested in acidic buffer 0.1N HCl of 900ml at 37 ±0.5˚C. Aliquot volume was withdrawn at 10, 20, 40 60,80,100 and 120 min and filtered through 0.45µ membrane filter. The samples were diluted with methanolic HCl and absorbance of the resulting sample was measured at 235 nm and 252 nm (Lambda max of Artemether is 252nm, lambda max of Lumefantrine is 235nm)

Fig. 4: Dissolution apparatus

PROCEDURE

- 7.5 gm of suspension powder contains 80 mg of ARM and 480 mg LUM.
- For Assay Weigh a suspension powder containing 100 mg of LUM and 16mg of ART and dissolve in 50ml of Conc. Methanolic HCL
- Kept on water shaker bath at 60 C for 1 Hr

- After 1 Hr filter and make up the final volume to 100ml with methanol now this solution is stock solution.
- From the stock solution 1ml was pipetted out and diluted to 10 ml
- Absorbance of this solution was taken at 252nm and 235 nm for Artemether and lumefantrine.
- Absorbance was taken using UV Spectrophotometer and drug content was calculated using simultaneous equations which was developed using method validation

Fig. 5: Dissolution

3.3. STABILITY TESTING(18,19)

ICH specifies the length of study and storage conditions.

- Long term testing 25°C ± 2°C /60 % RH ± 5% for 12 months
- Accelerated testing 40°C ± 2°C/75% RH ±5% for 6 months
- Refrigerated conditions 5°C ± 3°C. for 3 months

Stability studies for the present work was carried out at 25°C ± 2°C / 60% RH and 40°C ± 2°C / 75 % RH for the selected formulation for three months and at 5°C ± 3°C refrigerated conditions for 3 months.

METHOD

The selected formulations were packed in wide mouth bottle. They were stored at 25°± 2°C /60%± 5% RH and 40° ± 2°C /75%± 5% RH for 3 months in humidity chamber and evaluated for their physical appearance and drug content at specified intervals of time.

Fig. 6: stability

4. CONCLUSION:

Using Kneading method taste masked dry powder with good flow properties and stability was prepared, the reconstituted suspension had good viscosity, sedimentation volume, stability, pH and in vitro drug release properties. A fixed dose combination of dry powder ready for reconstitution formulation of Artemether and Lumefantrine was successfully developed that has in-vitro drug release characteristics same as compared to the marketed product. Since the prepared dry powder was taste masked the problem associated with patient compliance in case of marketed formulation was overcome. UV method was successfully developed and validated for the analysis of artemether and lumefantrine in the formulation The developed UV method provides simple, precise, sensitive and reproducible quantitative method for routine analysis of Artemether and Lumefantrine in the formulations. Based on the result, obtained from the analysis using described method, it can be concluded that the method has linear response in range of 4-20 µg/mL for Artemether and 2-10 µg/mL for Lumefantrine with co-efficient of correlation (r2) 0.995 for both artemether and lumefantrine. The prepared dry powder was confirmed to be taste masked by volunteers and DSC analysis The prepared dry powder had viscosity in the range of 1000-1400 cps which is adequate for oral administration The reconstituted suspension had acceptable organoleptic property, viscosity, pH, sedimentation volume, degree of flocculation. It is expected that this work will act as Benchmark for treatment of acute uncomplicated malaria caused by Plasmodium falciparum, including malaria acquired in chloroquine resistant area.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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