

# A New Approach: Micro-Emulsifying Suppository for Treatment of Malaria

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## ABSTRACT

Most of the drugs are administered through oral route. It has limited to such drug molecules which has poor solubility which is one of important parameters to achieve desired concentrations of drug in systemic circulations with desired pharmacological response. Self-micro emulsifying drug delivery system is new approach to improve the solubility of poorly soluble drugs which improves solubility thereby increases dissolution rate and bioavailability of drugs. SMEDDS is available as different dosage forms such as capsules, tablets, suppositories, and topical preparations. Suppositories usually melt, soften, or dissolve at body temperature which acts as a protectant or palliative to the local tissues at the point of introduction or as a carrier of therapeutic agents for systemic or local action. The self-micro emulsifying suppository offers more advantages over the other route of administrations.

**Keywords:** Suppository, Micro emulsion, Antimalarial.

## INTRODUCTION

Malaria is formidable disease in numerous tropical countries and it has many potential negative effects on economic growth and development.(1) It has been accounted for one to two million death across the globe every year consistently, In humans malaria is caused by four distinct parasites: Plasmodium vivax, Plasmodium falciparum, Plasmodium malaria and Plasmodium ovule.(2) .It starts with a bite from an infected female mosquito, which release saliva into the circulatory system, and ultimately to the liver where they mature and reproduce. As it mentioned that malaria begin in 2700 BC in China which prompts to decay of Roman empire. History shows Quinine first purified from tree bark in 1820, Charles Louis Alphonse Laveran identifies the malaria parasite in year 1880 later World Health Organization (WHO) launches Global Malaria Eradication Campaign in 1955.(3) Among these, the foremost severe protozoal infection is caused by blood-borne apicomplexan parasite P. falciparum that is accountable for the majority the malaria-related deaths. Some of the malarial symptoms consist of Fever, Cold, Rigor, Fatigue, Headache, Bitter-tongue, Vomiting, Diarrhoea, Convulsion, Anaemia, Jaundice ,Choluria, Hypoglycaemia, Prostration, and Hyperpyrexia.(4)

**PATHOLOGY:** Malaria parasite goes through two phases - an exoerythrocytic and an erythrocytic phase. Exoerythrocytic phase involves the maturation and growth of the parasite in the liver. At the point when contaminated mosquito transmits the infection or sporozoites as it takes in a blood meal the sporozoites in the mosquito's saliva enter the circulatory system and enter to the liver.

Erythrocytic phase includes the red blood cells in which merozoites multiply number of times asexually

and burst the red blood cells as they increase delivering the merozoites in blood. Each burst is related with a short period of fever.(5)

## MALARIAL PARASITE LIFE CYCLE

Malaria is a disease caused by single-cell, eukaryotic parasites from the genus Plasmodium. The definitive host of P. falciparum is the Anopheles mosquito which transmits parasites to the human host during a blood feed. Plasmodium life cycle begins when sporozoites enter the blood of the vertebrate host after being bitten by a mosquito which transmits a motile sporozoites enters through the blood. In liver sporozoites reproduce asexually produces thousands of merozoites called schizogony. All the clinical manifestations of malaria are associated with the asexual, intraerythrocytic replication of the parasites, highlighting the need to study the asexual lifecycle. Within the erythrocyte, the parasite feeds on host cell haemoglobin to support its own growth before replicating into 16–32 daughter parasites, known as merozoites infect red blood cells and formation of ring forms, trophozoites and schizonts. Merozoites develop into female and male gametes, Gametocytes are taken and mature in mosquito gut. Male and female gametocytes fuse and form ookinete which develop into new sporozoites that migrates to the insect's salivary glands.(6) After entering the erythrocyte, the cycle begins again: the parasite exports hundreds of proteins into the host to create its niche and imports haemoglobin to consume and prepare for a new round of replication. A subset of asexual parasites exits this replication cycle to develop into gametocytes that are taken up into a new mosquito host for sexual development and propagation to a new human host(7)

**Micro-emulsifying suppository** Children with extreme malaria frequently experience unconsciousness, convulsions, and vomiting, which makes administration of drug through oral difficult. In many cases, parenteral administration is impossible, due to lack of equipment and adequately trained staff, or potentially hazardous if adequate sanitization is not maintained. Rectal administration is often sought as an alternative route of administration to overcome the gastric irritation, nausea, and vomiting that may be associated with oral administration. Furthermore, drugs are administered rectally when the oral route is not convenient, as in infants and elderly patients(8) polyethylene glycol (PEG)-based suppository, which may soften or dissolves lately in the rectum and vagina due to its relatively high melting point, cannot be rapidly absorbed in the mucous membranes.(9)

**Composition of microemulsion** Oils, Surfactant, Co surfactant/Co solvent

**Surfactants:** Surfactants are formed by two parts with different affinities for the solvents, water (polar solvents) and oil phase (non-polar solvents). The surfactants used in self-emulsifying formulations are known to increase the bioavailability by various mechanisms including: increased intestinal epithelial permeability, improved dissolution increased tight junction permeability to GIT.

Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Labrasol, Polyoxy-40- hydrogenated castor oil (Cremophor RH40), D-alpha Tocopherol polyethylene glycol 1000 succinate, Lauromacrogol 300, Lecithins, Decyl polyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oblique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG- 8 caprylic/capril glyceride (Labrasol).(10)

**Co-surfactant/Co-solvents:** It help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base.

Span 20, Span 80, Caproyl 90, Capmul, Ethanol, Polypylene glycol, Polyethylene glycol, Sorbitan monooleate, Sorbitan monostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90)

Oils can solubilize the lipophilic medication in a specific amount. Increase in the sum of lipophilic drug transported via the intestinal lymphatic system, subsequently increase in the absorption from the GI tract. Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been utilised as the oil phase. Lipophilic drugs are preferably solubilized in o/w microemulsions. The main principle for selecting the oil phase is that the drug should have high solubility in it. (11)

Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Sesame oil, Peanut oil, Labrafac, Labrafil, Castor oil, Ethyl oleate, Mineral oil, Isopropyl myristate, Decanol, Oleic acid, Vegetable oils (Coconut oil, Safflower oil, Soyabean oil, Olive oil)

### Preparation of microemulsion

Appropriate volume of water was added to a weighed amount of surfactant. The mixture was gently stirred, and it was initially slurry. A calculated volume of oil was then added and this produced a two-phase system. After that a cosurfactant was added drop-wise while the system is being stirred. The samples were then stirred for 15 min to allow equilibration, after a given amount of cosurfactant was added, a clear isotopic solution was obtained. This system remained clear and homogeneous for a long time. This signifies its thermodynamic stability.(12)

### Composition of suppositories

#### Suppository bases:

**Cocoa butter:** It is plant-based fat, pale-yellowish solid with a mild odour and bland taste. Cocoa butter is the fat from the seeds of *Theobroma cacao* (cocoa beans). It is acquired by expressing the oil from the seeds or by solvent extraction. It is insoluble in water, slightly soluble in alcohol, and soluble in boiling absolute alcohol.

**Glycerinated gelatin bases:** This base consists of 70 parts of glycerine, 20 parts of gelatin, and 10 parts of water. The base material has a soft, rubbery consistency which makes them suitable for vaginal administration but not firm enough for rectal use.

**Polyethylene glycol bases:** Polyethylene glycol (PEG) suppository bases are composed of blends of polyethylene glycol polymers of various molecular weights

It has been notified as water soluble drugs have better release profile from fatty base than from a water-soluble base. Two fatty bases were therefore considered for the study: Cocoa butter and Fattibase™.

Cocoa butter is available locally and also affordable. When heated, cocoa butter liquefies in 3-7 minutes. Cocoa Butter or *Theobroma Oil* is an oleaginous base that softens at 30C and melts at 34C. Cocoa Butter will melt to form non-viscous, bland oil. The lower melting point polymorphs will convert to the more stable form over time. When overheated, the suppository will stick to the mould and release will be difficult.(13)

## Preparation of suppositories

Some investigators proved that solid-SEDDs could not only increase the GI absorption but also increase the rectal/vaginal adsorption. Glycyrrhizin, hardly achieves therapeutic plasma concentrations by oral route, but can achieve acceptable therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories.(10)

Suppositories were prepared using the fusion method following an earlier described method using a blend of polyethylene glycols (PEG1000, PEG4000) as the suppository base. Prior to incorporation into the base, the drug powder was passed through a 100-mm mesh sieve. Sodium salicylate was micronized and also passed through the same sieve.(14) Briefly, 4 g of PEG3350 and 11 g of PEG 1000 were mixed together, melted at 60°C on a hot plate, and cooled down to 50°C. Then, 500 mg of drug was added to the melted PEG mixture and stirred until uniformly dispersed. The mixture was poured into four cavities of an aluminium suppository mold and allowed to solidify at room temperature (25°C). Suppositories were removed from the mold, numbered, and measured for weights, heights, and widths. (15)(16)

## Evaluations

### Physical appearance:

For Physical appearance microemulsion can be inspected visually for homogeneity, fluidity and optical clarity.(17)

### Drug stability:

The optimized microemulsion was kept under cold condition (4-8°C), room temperature and at elevated temperature (50 ± 2 °C).(17)

### Globule size and zeta potential measurements:

The globule size and zeta potential of the microemulsion can be determined by dynamic light scattering, using a Zetasizer HSA 3000.(18)

### Permeability and Absorption:

BCS class II antimalarial drugs often reported to be highly permeable or borderline high-to-low permeable. The absolute BA after oral quinine intake was reported to be 76% or 88%, indicating that quinine has good permeability.

Drug was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 24 h at room temperature, samples were withdrawn and centrifuged at 6000 rpm for 10 min. The amount of soluble drug in the optimized formulation as well as each individual ingredient of the formulation was calculated by subtracting the

drug present in the sediment from the total amount of drug added.(15)

### Determination of Disintegration Time and Self-Micro emulsification Time:

Self-emulsifying suppositories emulsify easily in disintegration medium while PEG suppositories slowly dissolve and melt. Hence, in comparison to developed SMES, PEG-based suppositories demonstrated a higher disintegration time which could also be described to the higher melting points of the suppository base. Conversely, SMES showed rapid micro emulsification time justifying its short disintegration time(15)

### Particle size determination

The 10- and 15-micron particles were not uniformly dispersed in the suppositories. The suppositories had a mottled appearance.(15)

### Test of appearance

There should be no differences in size or shape among the suppositories. The suppositories should have an elegant appearance. Cracks and pits can occur due to air being trapped in the molten mass. Examine each suppository separately for signs of air entrapment.

### Breakage test (Test of physical strength)

The tensile strength of the bundles of suppositories is measured to assess their resistance to normal handling. Testing is conducted using an apparatus called a breaking test apparatus.

There are two walls to this apparatus.

This chamber pumps water through its walls. Suppositories are contained inside a disc in the inner chamber. It is connected by a rod. Alternatively, the end of the rod is made up of another disc that contains weights

Test of dissolution rate Dissolution of dosage forms occurs over an extended period in body fluid. It measures the rate at which the medication leaves the suppository. (19)

The dissolution rate can be determined using two different types of instruments.

They are Suppository dialysis cells - To further define the characteristics of lipophilic suppositories, suppository dialysis cells are used. Subsequently, modified flow-through cells are used to test lipophilic suppositories.

Stationary basket - Located in the stationary basket is a rotating paddle apparatus (USP dissolution test apparatus). Suppositories with hydrophilic properties are tested with a rotating paddle basket apparatus.

### Test of melting range

A micro melting range is determined the same way as a macro melting range:

**Macro melting range:** The thermal stability of a suppository is measured by this parameter. Melting the suppository over a given period is carried out in an environment of constant temperature. A tablet disintegration apparatus is used for the test. Water is continuously poured over the suppository during the test. This is followed by a melting investigation.

## CONCLUSION

Self-Micro Emulsifying Drug Delivery Systems seems to be a novel and commercially a viable option to the issue of low oral bioavailability based on by lipophilic drugs. It is one approach for improving the oral bioavailability of medications since there is an increase in the oral drug absorption of BCS II class drugs. The landscape of the malarial prevention and treatment field is constantly changing as new data emerge. As such the field needs to be able to adapt to those needs. Current development has moved away from traditional suppository formulations. Therefore, other dosage forms, such as micro emulsifying suppositories have gained significant interest. However, in the antimalarial research and development field, there has been little advancement in the field of rectal drug delivery.

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Micro melting range Capillary tubes are used to measure the melting range of a fatty base.

## Liquefaction time (Softening)

The softening time refers to the time that it takes for the suppository to melt completely at a certain temperature. As a result of this test, the softening time of suppositories can be estimated, which describes the hardness of the basis.(20)

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