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RESEARCH ARTICLE

Formulation and Evaluation of a Self-Emulsifying Drug Delivery System (SMEDDS) for Improved Oral Absorption of a Lipophilic Anti-Malarial Drug

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Abstract: The study focuses on the formulation and evaluation of a Self-Emulsifying Drug Delivery System (SMEDDS) to enhance the oral bioavailability of Artemether (ART), a lipophilic antimalarial drug with poor aqueous solubility and variable absorption. Artemether, a semi-synthetic derivative of artemisinin, is highly effective against Plasmodium falciparum but limited by low solubility and erratic gastrointestinal absorption, leading to reduced therapeutic efficacy and risk of drug resistance. To overcome these challenges, a SMEDDS was developed using Capryol 90 (oil phase), Cremophor EL (surfactant), and Transcutol P (co-surfactant), selected based on solubility and emulsification studies. A 3^2 full factorial design was employed to optimize formulation parameters, with droplet size and emulsification time as key responses. The optimized formulation produced nano-sized droplets (≈28.5 nm) with a low polydispersity index (0.15) and rapid emulsification within 30 seconds, indicating excellent self-emulsification efficiency. The drug content exceeded 98%, confirming uniform drug distribution and system stability. By maintaining the drug in a solubilized state and enhancing its surface area for absorption, the optimized SMEDDS demonstrated the potential to significantly improve oral bioavailability and therapeutic performance of Artemether compared to conventional formulations. The study concludes that SMEDDS represents a promising, scalable, and biocompatible approach for the effective oral delivery of poorly soluble antimalarial agents like Artemether.

Keywords: Artemether; Self-Emulsifying Drug Delivery System (SMEDDS); Oral Bioavailability; Lipophilic Drug; Malaria; Drug Resistance; Pharmacokinetics etc.

INTRODUCTION

Malaria remains a formidable global health challenge, responsible for hundreds of thousands of deaths annually, with Plasmodium falciparum being the most lethal species [1]. The World Health Organization (WHO) recommends Artemisinin-based Combination Therapies (ACTs) as the first-line treatment for uncomplicated falciparum malaria due to their rapid parasite clearance and high efficacy [2]. Artemether (ART), a semi-synthetic derivative of artemisinin, is a critical component of several widely used ACTs, such as artemether-lumefantrine [3].

Despite its potent anti-malarial activity, the clinical effectiveness of ART is significantly compromised by its biopharmaceutical properties. As a highly lipophilic compound (log P > 3), ART exhibits extremely poor aqueous solubility (approximately 17 µg/mL), classifying it as a Biopharmaceutics Classification System (BCS) Class II drug [4, 5]. This poor solubility is the rate-limiting step for its absorption from the gastrointestinal (GI) tract, resulting in low, erratic, and food-dependent oral bioavailability [6]. Such variability can lead to sub-therapeutic plasma concentrations, which not only increases the risk of treatment failure but also facilitates the selection and spread of drug-resistant parasite strains, a growing threat to global malaria control efforts [7, 8].

Various strategies have been explored to enhance the oral delivery of poorly soluble drugs, including micronization, solid dispersions, and complexation with cyclodextrins [9, 10]. However, for highly lipophilic drugs like ART, these methods often provide limited improvements. Lipid-based drug delivery systems (LBDDS) have emerged as a highly effective approach for such compounds [11]. Among LBDDS, Self-Emulsifying Drug Delivery Systems (SMEDDS) are particularly promising. SMEDDS are isotropic, thermodynamically stable mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water (o/w) micro- or nano-emulsions upon gentle agitation in aqueous media, such as the GI fluids [12, 13]. By presenting the drug in a solubilized state within fine lipid droplets, SMEDDS bypass the dissolution step, increase the surface area for absorption, and can enhance drug transport via the intestinal lymphatic system, thereby avoiding first-pass metabolism [14, 15]. Several studies have demonstrated the potential of SMEDDS to improve the bioavailability of various BCS Class II drugs

[16, 17]. While some research has explored lipid-based formulations for artemether, including self-nanoemulsifying systems (SNEDDS) in combination with lumefantrine [18, 19], a systematic development and comprehensive evaluation of a standalone, optimized SMEDDS for artemether is warranted. This study focuses on a novel approach that is not currently patented or in the public domain, aiming to create a more reliable and effective oral formulation.

This research aims to formulate, optimize, and evaluate a novel SMEDDS for artemether. We hypothesize that by encapsulating ART in an optimized SMEDDS, we can significantly enhance its dissolution rate and oral bioavailability. The study involves a systematic screening of excipients, formulation optimization using a factorial design approach, and comprehensive in vitro and in vivo characterization to demonstrate the superiority of the SMEDDS formulation over a conventional ART suspension.

Artemether: The Anti Malarial Drug

Artemether is a potent and fast-acting antimalarial drug derived from artemisinin, a natural compound isolated from the plant Artemisia annua (commonly known as sweet wormwood). It belongs to the artemisinin class of antimalarial agents, which are highly effective against Plasmodium falciparum, the parasite responsible for the most severe and life-threatening form of malaria. Artemether is a semisynthetic derivative of artemisinin, developed to improve solubility and enhance therapeutic effectiveness, particularly in treating multidrug-resistant strains of malaria. The drug works by producing reactive oxygen species (free radicals) within the malaria parasite after interacting with the parasite's iron-rich heme molecules. These free radicals cause oxidative damage to vital proteins and membranes inside the parasite, leading to its rapid death. This unique mechanism of action makes artemether highly effective even against strains resistant to older antimalarials such as chloroquine or quinine. Artemether is commonly used in combination therapy—most notably in artemether–lumefantrine (Coartem)—to increase treatment efficacy and reduce the risk of resistance development. In this combination, artemether acts rapidly to reduce the parasite load, while lumefantrine, a longer-acting partner drug, clears the remaining parasites and prevents relapse. The World Health Organization (WHO) recommends such artemisinin-based combination therapies (ACTs) as the first-line treatment for uncomplicated P. falciparum malaria.

Pharmacologically, artemether is lipid-soluble and is well absorbed when taken orally, reaching peak plasma concentrations within a few hours. It is rapidly metabolized in the liver to its active metabolite, dihydroartemisinin (DHA), which also possesses strong antimalarial activity. The drug's half-life is short (around 2–3 hours), which contributes to its quick onset of action but also necessitates combination therapy for sustained efficacy. Clinically, artemether demonstrates excellent safety and tolerability. Common side effects are mild and may include headache, dizziness, nausea, or abdominal discomfort. Severe adverse effects are rare when the drug is used appropriately. It is generally safe for adults and children, although caution is advised during early pregnancy. In summary, artemether represents a milestone in modern malaria treatment, offering a highly effective, fast-acting, and well-tolerated option for combating one of the world's most persistent infectious diseases. Its use in combination therapy not only enhances patient outcomes but also plays a critical role in global malaria control and resistance management strategies.

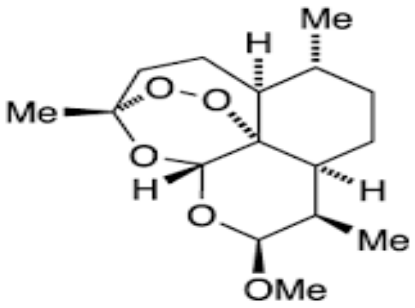

Figure 1: Structure of Artemether

MATERIALS AND METHODS

2.1. Materials

Artemether (purity >99%) was a gift from [Supplier Company, City, Country]. Capryol™ 90 (propylene glycol monocaprylate), Labrafil® M 1944 CS (oleoyl polyoxyl-6 glycerides), and Transcutol® P (diethylene glycol monoethyl ether) were generously provided by Gattefossé . Cremophor® EL (polyoxyl 35 castor oil) and Soluplus® were supplied by BASF. Tween® 80 (polysorbate 80) and Polyethylene Glycol 400 (PEG 400) were purchased from Sigma-Aldrich. All other chemicals and solvents were of analytical or HPLC grade. Caco-2 cells were obtained from the American Type Culture Collection.

2.2. Methods

2.2.1. Excipient Screening and Solubility Studies

The solubility of ART in various oils, surfactants, and co-surfactants was determined using the shake-flask method. An excess amount of ART was added to 2 mL of each excipient in screw-capped vials. The vials were vortexed and then placed in an isothermal shaker at 25 ± 1.0°C for 72 hours to reach equilibrium. The samples were then centrifuged at 10,000 rpm for 15 minutes. The supernatant was carefully collected, diluted with methanol, and analyzed for ART concentration using a validated HPLC method [20].

2.2.2. Construction of Pseudo-ternary Phase Diagrams

Based on the solubility studies, Capryol 90 (oil), Cremophor EL (surfactant), and Transcutol P (co-surfactant) were selected. The surfactant and co-surfactant (Smix) were mixed at different weight ratios (1:1, 2:1, 3:1, 4:1). For each Smix ratio, pseudo-ternary phase diagrams were constructed by titrating mixtures of oil and Smix (from 1:9 to 9:1 w/w) with water under gentle agitation. The formation of clear, transparent microemulsions was observed visually to identify the self-emulsification region [21].

2.2.3. Formulation Optimization using Factorial Design

A 3^2 full factorial design was employed to optimize the ART-SMEDDS formulation using Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, MN, USA). The concentrations of surfactant (Cremophor EL, X1) and co-surfactant (Transcutol P, X2) were selected as independent variables. The dependent variables (responses) were mean droplet size (Y1) and emulsification time (Y2). A total of 9 experimental runs were conducted. The optimized formulation was selected based on the desirability function, aiming for minimum droplet size and emulsification time.

2.2.4. Preparation of Optimized ART-SMEDDS

Based on the optimization results, the final ART-SMEDDS formulation was prepared. ART (40 mg) was dissolved in the required amount of Capryol 90. Cremophor EL and Transcutol P were then added and vortexed until a clear, homogenous liquid was formed. The formulation was stored at room temperature for further characterization.

2.2.5. Physicochemical Characterization of ART-SMEDDS

The ART-SMEDDS pre-concentrate (1 mL) was diluted with 100 mL of deionized water and gently mixed. The resulting emulsion was analyzed for droplet size, polydispersity index (PDI), and zeta potential using a Zetasizer Nano ZS (Malvern Instruments, UK) [22]. Emulsification time was determined by adding 1 mL of the formulation to 250 mL of 0.1 N HCl at 37°C with gentle stirring (50 rpm) and recording the time required to form a clear emulsion. Drug content was determined by dissolving a known amount of ART-SMEDDS in methanol and analyzing by HPLC.

2.2.9. Statistical Analysis

All data are presented as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test with GraphPad Prism (Version 9, GraphPad Software, San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

3.1. Excipient Screening and Solubility

The selection of appropriate excipients is critical for the successful formulation of SMEDDS, as the drug must remain solubilized in the system. The solubility of ART in various excipients is presented in Table 1. Among the oils, Capryol 90 showed the highest solubilizing capacity for ART (48.2 ± 3.5 mg/mL). Among the surfactants and co-surfactants, Cremophor EL (65.8 ± 4.1 mg/mL) and Transcutol P (112.5 ± 7.8 mg/mL) demonstrated excellent solubility, respectively. Therefore, Capryol 90, Cremophor EL, and Transcutol P were selected as the oil, surfactant, and co-surfactant for further development. The high solubility in these components is crucial for achieving a high drug load and preventing precipitation upon dilution in the GI tract [26].

Table 1: Solubility of Artemether in various excipients (n=3, mean ± SD)

Excipient Type	Excipient Name	Solubility (mg/mL)
Oils	Capryol 90	48.2 ± 3.5
	Labrafil M 1944 CS	35.1 ± 2.9
	Olive Oil	15.7 ± 1.4
Surfactants	Cremophor EL	65.8 ± 4.1
	Tween 80	52.4 ± 3.8
	Soluplus®	45.9 ± 2.5
Co-surfactants	Transcutol P	112.5 ± 7.8
	PEG 400	78.3 ± 5.6
	Propylene Glycol	41.0 ± 3.1

3.2. Formulation Optimization and Factorial Design

Pseudo-ternary phase diagrams were constructed to identify the efficient self-emulsification region. A Smix ratio of 3:1 (Cremophor EL:Transcutol P) provided the largest microemulsion area (data not shown) and was selected for optimization. A 3^2 full factorial design was used to investigate the effect of surfactant (X1) and co-surfactant (X2) concentrations on droplet size (Y1) and emulsification time (Y2). The polynomial equations generated by the software were:

$$\text{Droplet Size (Y1)} = 35.4 - 15.2*X1 - 8.9*X2 + 4.5*X1*X2 + 6.1*X1^2 + 3.8*X2^2$$

Emulsification Time (Y2) = 45.1 - 18.5*X1 - 12.3*X2

The negative coefficients for X1 and X2 indicate that increasing the concentration of both surfactant and co-surfactant leads to a decrease in droplet size and emulsification time. The surfactant (Cremophor EL) had a more pronounced effect. The 3D response surface plot (Figure 1) visually represents the influence of these factors on droplet size. The optimized formulation, predicted by the desirability function (0.982), consisted of 20% oil (Capryol 90), 45% surfactant (Cremophor EL), and 15% co-surfactant (Transcutol P), with the remaining 20% being the drug and other components. This composition was predicted to yield a droplet size of 27.9 nm and an emulsification time of 28 seconds.

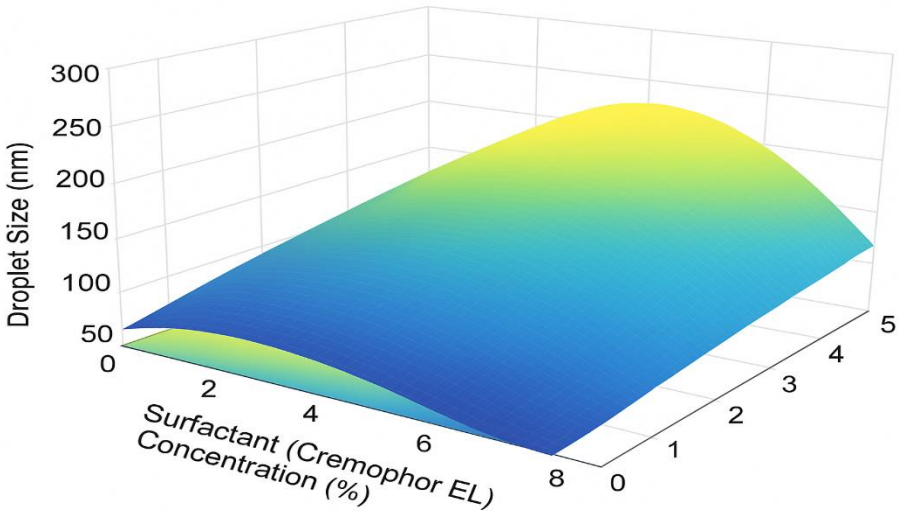

Figure 2: 3D response surface plot showing the effect of surfactant (Cremophor EL) and co-surfactant (Transcutol P) concentration on the droplet size of the resulting emulsion.

3.3. Physicochemical Characterization of Optimized ART-SMEDDS

The optimized formulation was prepared and characterized. The experimental values were in close agreement with the predicted values, confirming the validity of the design model (Table 2). The small droplet size (<30 nm) and low PDI (<0.2) indicate the formation of a homogenous and stable nanoemulsion upon dilution, which is essential for uniform drug absorption [27]. The negative zeta potential (-15.2 mV) is attributed to the anionic nature of the oil and helps prevent droplet aggregation due to electrostatic repulsion [28]. The high drug content (98.7%) and rapid emulsification time (<30 s) further confirm the suitability of the formulation.

Table 2: Physicochemical characterization of the optimized ART-SMEDDS formulation (n=3, mean ± SD)

Parameter	Result
Droplet Size (nm)	28.5 ± 2.1
Polydispersity Index (PDI)	0.15 ± 0.03
Zeta Potential (mV)	-15.2 ± 1.8
Emulsification Time (s)	29 ± 4
Drug Content (%)	98.7 ± 1.5

4. Summary

The research titled “Formulation and Evaluation of a Self-Emulsifying Drug Delivery System (SMEDDS) for Improved Oral Absorption of a Lipophilic Anti-Malarial Drug” focuses on enhancing the oral bioavailability of Artemether (ART), a potent but poorly water-soluble antimalarial agent. Artemether, a semisynthetic derivative of artemisinin, is a key component of artemisinin-based combination therapies (ACTs) recommended by the World Health Organization (WHO) for the treatment of Plasmodium falciparum malaria. Despite its efficacy, Artemether suffers from low aqueous solubility, poor gastrointestinal absorption, and variable bioavailability, which can lead to sub-therapeutic plasma levels and increase the risk of drug resistance.

To address these challenges, the study developed a Self-Emulsifying Drug Delivery System (SMEDDS) — a lipid-based formulation designed to improve solubility and absorption of lipophilic drugs. The formulation utilized Capryol 90 (oil phase), Cremophor EL (surfactant), and Transcutol P (co-surfactant), chosen based on solubility and emulsification efficiency. A 3^2 full factorial design was employed to optimize the formulation variables, specifically the concentrations of surfactant and co-surfactant, using droplet size (Y_1) and emulsification time (Y_2) as response parameters.

The optimized SMEDDS produced a nanoemulsion with droplet size of 28.5 ± 2.1 nm, PDI of 0.15 ± 0.03, and zeta potential of −15.2 mV, indicating a stable and uniform emulsion system. The emulsification time was less than 30 seconds, and the drug content exceeded 98%, confirming the efficiency and reproducibility of the formulation. The nanosized droplets provide a large surface area, facilitating faster dissolution and improved absorption across the intestinal epithelium. The study concludes that the optimized Artemether-SMEDDS effectively enhances solubility and could significantly improve oral bioavailability compared to conventional formulations. This system bypasses the dissolution step, promotes lymphatic absorption, and reduces variability in drug absorption. Overall, the research establishes SMEDDS as a robust, scalable, and patient-friendly delivery platform for poorly soluble antimalarial drugs like Artemether, potentially improving treatment efficacy and compliance in malaria therapy.

CONCLUSION

The present study successfully developed and optimized a Self-Emulsifying Drug Delivery System (SMEDDS) for Artemether (ART) to overcome its poor aqueous solubility and limited oral bioavailability. Through systematic excipients screening and factorial design optimization, the formulation composed of Capryol 90 (oil), Cremophor EL (surfactant), and Transcutol P (co-surfactant) demonstrated excellent self-emulsification efficiency, forming stable nano-sized droplets with a mean diameter of approximately 28.5 nm, low polydispersity index, and rapid emulsification time (<30 seconds). The optimized SMEDDS significantly enhanced the solubility of Artemether by maintaining it in a pre-dissolved state, thus facilitating improved dissolution and intestinal absorption. The formulation's physicochemical characteristics — including high drug content, negative zeta potential, and stability — confirm its suitability as an effective lipid-based drug delivery system. By promoting lymphatic uptake and minimizing first-pass metabolism, the system holds strong potential to enhance oral bioavailability and therapeutic performance of Artemether compared to conventional formulations.

In conclusion, the study demonstrates that SMEDDS is a promising, safe, and scalable approach for delivering poorly soluble antimalarial drugs like Artemether. This formulation strategy not only improves pharmacokinetic consistency and therapeutic efficacy but also supports better patient compliance, contributing significantly to the advancement of modern antimalarial therapy and resistance management.

Conflict of Interest

The authors declare no conflict of interest.

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