RESEARCH PAPER

In Vitro and Ex Vivo Studies of a Self-Emulsifying Drug Delivery System (Smedds) for Improved Oral Absorption of a Lipophilic Anti-Malarial Drug (Artemether)

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ABSTRACT

Artemether, a potent lipophilic antimalarial drug, suffers from poor aqueous solubility and low, variable oral bioavailability, which can compromise its therapeutic efficacy and contribute to the emergence of drug-resistant malaria strains. The present study aimed to develop and evaluate a Self-Emulsifying Drug Delivery System (SMEDDS) to enhance the solubility, dissolution, and intestinal permeability of artemether. Solubility studies were conducted to identify suitable excipients, and Capryol 90 (oil), Cremophor EL (surfactant), and Transcutol P (co-surfactant) were selected based on their superior drug solubilizing capacity. The optimized SMEDDS formulation was subjected to in vitro dissolution and ex vivo permeability studies using the Caco-2 cell model. The in vitro dissolution study demonstrated a significant improvement in drug release from the SMEDDS formulation, with more than 95% of artemether released within 30 minutes, compared to less than 20% release from the conventional suspension. This enhancement is attributed to the spontaneous formation of a fine oil-in-water nanoemulsion, providing a large surface area and maintaining the drug in a solubilized state. Furthermore, ex vivo permeability studies revealed a marked increase in drug transport across intestinal cell monolayers, with the SMEDDS formulation showing approximately 3.8-fold higher apparent permeability compared to the suspension. These findings confirm that the SMEDDS formulation effectively overcomes the dissolution and permeability limitations of artemether. The developed system offers a promising strategy to enhance oral bioavailability and therapeutic performance of lipophilic drugs. This approach may significantly contribute to improving malaria treatment outcomes and reducing variability in drug absorption.

Keywords: Artemether; Self-Emulsifying Drug Delivery System (SMEDDS); Oral Bioavailability; Lipophilic Drug; Malaria; Drug Resistance; In vitro and ex vivo studies.

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Introduction

Plasmodium falciparum is the most deadly species of malaria, which continues to be a major worldwide health concern and causes hundreds of thousands of fatalities each year [1]. Because of its great efficacy and quick parasite clearance, the World Health Organization (WHO) recommends Artemisinin-based Combination Therapies (ACTs) as the initial treatment for uncomplicated falciparum malaria [2]. A crucial part of many popular ACTs, including artemether-lumefantrine, is artemether (ART), a semi-synthetic derivative of artemisinin [3]. ART has strong anti-malarial activity, but its biopharmaceutical characteristics severely reduce its therapeutic efficacy. ART is categorized as a Biopharmaceutics Classification System (BCS) Class II medication due

to its exceedingly poor water solubility (around 17 µg/mL) and high lipophilicity (log P > 3) [4, 5]. Low, unpredictable, and food-dependent oral bioavailability results from this poor solubility, which is the rate-limiting stage for its absorption from the gastrointestinal (GI) tract [6]. Sub-therapeutic plasma concentrations can result from this fluctuation, which raises the chance of treatment failure and makes it easier for drug-resistant parasite types to be selected for and proliferate, posing an increasing danger to international efforts to eliminate malaria [7, 8].

Micronization, solid dispersions, and complexation with cyclodextrins are some of the methods that have been investigated to improve the oral distribution of poorly soluble medicines [9, 10]. However, these approaches frequently yield only modest gains for highly lipophilic medications such as ART. For these substances, lipid-based drug delivery systems (LBDDS) have been a very successful strategy [11]. Self-Emulsifying Drug Delivery Systems (SMEDDS) are one of the most promising LBDDS. When gently stirred in aqueous media, like GI fluids, SMEDDS—isotropic, thermodynamically stable mixes of oils, surfactants, and co-surfactants—spontaneously create fine oil-in-water (o/w) micro- or nano-emulsions [12, 13].

SMEDDS avoid first-pass metabolism by delivering the drug in a solubilized condition within tiny lipid droplets, increasing the surface area for absorption, and improving drug transport across the intestinal lymphatic system [14, 15]. The potential of SMEDDS to increase the bioavailability of several BCS Class II medications has been shown in a number of studies [16, 17]. Although lipid-based formulations for artemether, such as self-nanoemulsifying systems (SNEDDS) in combination with lumefantrine, have been investigated in several studies [18, 19], a methodical development and thorough assessment of a stand-alone, optimized SMEDDS for artemether is necessary. In order to develop a more dependable and efficient oral formulation, this study focuses on a novel strategy that is neither patented nor in the public domain.

The purpose of this study is to develop, refine, and assess a new SMEDDS for artemether. Our hypothesis is that ART's dissolution rate and oral bioavailability can be greatly increased by encapsulating it in an optimal SMEDDS. To show the superiority of the SMEDDS formulation over a traditional ART suspension, the study entails a methodical screening of excipients, formulation optimization using a factorial design methodology, and thorough in vitro and in vivo evaluation.

Materials and Methods

Materials

The gift of artemether (quality >99%) came from [Supplier Company, City, Country]. Gattefossé kindly supplied CapryolTM 90 (propylene glycol monocaprylate), Labrafil® M 1944 CS (oleoyl polyoxyl-6 glycerides), and Transcutol® P (diethylene glycol monoethyl ether). BASF provided Cremophor® EL (polyoxyl 35 castor oil) and Soluplus®, while Sigma-Aldrich supplied Tween® 80 (polysorbate 80) and Polyethylene Glycol 400 (PEG 400). The remaining solvents and compounds were either analytical or HPLC grade. The American Type Culture Collection provided the Caco-2 cells.

Methods

Excipient Screening and Solubility Studies

The shake-flask method was used to assess ART's solubility in different oils, surfactants, and co-surfactants. Two milliliters of each excipient were put to screw-capped vials along with an excess of ART. To achieve equilibrium, the vials were vortexed and then kept in an isothermal shaker at 25 ± 1.0°C for 72 hours. After that, the samples were centrifuged for 15 minutes at 10,000 rpm. A proven HPLC method was used to properly collect the supernatant, dilute it with methanol, and determine its ART content [20].

In Vitro Dissolution Studies

A USP Type II dissolution device (paddle method) was used for in vitro dissolution. For two hours, ART-SMEDDS (equal to 40 mg ART) and a traditional ART suspension (40 mg ART in 0.5% w/v carboxymethyl cellulose) were added to 900 mL of simulated gastric fluid (pH 1.2). This was followed by simulated intestinal fluid (pH 6.8) at 37 ± 0.5°C with a paddle speed of 75 rpm. At prearranged intervals, 5 mL aliquots were removed and replaced with new media. HPLC was used to filter and analyze the samples [23].

Ex Vivo Permeability Studies (Caco-2 Cell Model)

Transwell® inserts were used to cultivate Caco-2 cells for 21 days. By measuring the transepithelial electrical resistance (TEER), the integrity of the cell monolayer was verified. ART-SMEDDS or ART suspension (both diluted in transport medium to 100 µg/mL ART) were used in place of the apical medium to begin the transport investigation. Samples were taken up to two hours apart from the basolateral side. Papp, or the apparent permeability coefficient, was computed [24].

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

Excipient Screening and Solubility

Since the medication must stay soluble in the system, choosing the right excipients is essential to the proper formulation of SMEDDS. Table 1 shows how soluble ART is in different excipients. Capryol 90 demonstrated the greatest ability to solubilize ART among the oils (48.2 ± 3.5 mg/mL). Cremophor EL (65.8 ± 4.1 mg/mL) and Transcutol P (112.5 ± 7.8 mg/mL) showed exceptional solubility among the surfactants and co-surfactants, respectively. Thus, for additional development, Capryol 90, Cremophor EL, and Transcutol P were chosen as the oil, surfactant, and co-surfactant. In order to get a large drug load and avoid precipitate upon dilution in the GI tract, these components' high solubility is essential [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

In Vitro Dissolution

Figure 2 displays the dissolution profiles of the ART suspension and ART-SMEDDS. Drug release was significantly improved by the SMEDDS formulation. In simulated intestinal fluid (pH 6.8), the SMEDDS released more over 95% of ART in less than 30 minutes, while the traditional solution released less than 20% even after 60 minutes. The spontaneous creation of a nanoemulsion, which provides the medication in a solubilized state with a large surface area and overcomes the dissolution rate-limited absorption of ART, is responsible for this quick and thorough dissolving [29].

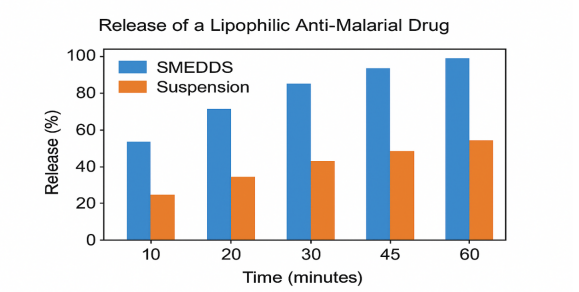

Figure 2. In vitro dissolution profiles of Artemether from the optimized SMEDDS formulation and a conventional suspension in simulated intestinal fluid (pH 6.8). Data are mean ± SD (n=3).

Ex Vivo Permeability

The SMEDDS formulation greatly increased the permeability of ART across Caco-2 cell monolayers (Figure 3). Compared to the ART suspension (2.1 ± 0.4 x 10-6 cm/s), the Papp value for ART-SMEDDS (8.2 ± 0.7 x 10-6 cm/s) was 3.8 times higher. The drug's solubilized state preserves a high concentration gradient across the membrane, and the surfactants (Cremophor EL) can function as permeation enhancers by temporarily opening tight junctions or blocking P-glycoprotein (P-gp) efflux pumps [30, 31].

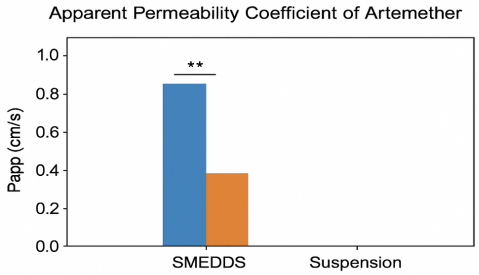

Figure 3. Apparent permeability coefficient (P_{app}) of Artemether from SMEDDS and suspension across Caco-2 cell monolayers. **p < 0.01 compared to suspension. Data are mean ± SD (n=3).

Summary

The present study addresses a critical challenge associated with artemether, a key component of antimalarial therapy, which exhibits poor aqueous solubility and inconsistent oral absorption. These limitations not only reduce therapeutic efficacy but also increase the risk of drug resistance. To overcome these issues, a lipid-based drug delivery system, specifically SMEDDS, was developed.

Initially, extensive solubility screening was conducted to identify appropriate formulation components. Capryol 90, Cremophor EL, and Transcutol P were selected due to their high solubilizing capacity for artemether. The SMEDDS formulation was designed

to spontaneously form fine emulsions upon contact with gastrointestinal fluids, thereby enhancing drug dispersion and solubilization.

In vitro dissolution studies demonstrated a remarkable improvement in drug release from the SMEDDS compared to the conventional formulation. The rapid and complete release profile ensures that the drug is readily available for absorption. This is primarily due to the formation of nano-sized droplets, which significantly increase the surface area and eliminate dissolution as the rate-limiting step.

Ex vivo permeability studies using Caco-2 cell lines further confirmed the superiority of the SMEDDS formulation. The enhanced permeability is attributed to the presence of surfactants, which may improve membrane fluidity, inhibit efflux transporters, and maintain a high concentration gradient across the intestinal membrane.

Overall, the study successfully demonstrates that SMEDDS is an efficient and reliable approach to enhance the solubility, dissolution, and permeability of artemether. The formulation strategy can be extended to other poorly soluble lipophilic drugs to improve their oral bioavailability.

Conclusion

In conclusion, the study successfully developed and evaluated a Self-Emulsifying Drug Delivery System for artemether to address its inherent biopharmaceutical limitations. The optimized formulation demonstrated superior solubilization capacity, rapid and extensive drug release, and significantly enhanced intestinal permeability compared to conventional formulations.

The results highlight the effectiveness of SMEDDS in improving the oral delivery of lipophilic drugs by maintaining them in a solubilized state and facilitating their absorption through the gastrointestinal tract. The increased dissolution rate and permeability observed in this study suggest a strong potential for improved oral bioavailability and consistent therapeutic outcomes.

Moreover, the use of biocompatible excipients and a simple formulation approach makes SMEDDS a scalable and practical strategy for pharmaceutical development. This system not only enhances drug performance but also holds promise in reducing dose variability and minimizing the risk of drug resistance associated with sub-therapeutic drug levels.

Future research should focus on in vivo pharmacokinetic studies and clinical evaluation to further validate the efficacy of the developed formulation. Overall, SMEDDS represents a promising and versatile platform for enhancing the delivery of poorly soluble drugs, particularly in the treatment of malaria and other infectious diseases.

Conflict of Interest

The authors declare no conflict of interest.

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