

Original Research

Developing Self-Nanoemulsifying Drug Delivery Systems Comprising an Artemether–Lumefantrine Fixed-Dose Combination to Treat Malaria

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Abstract

Background: Despite attempts to control malaria, poor drug bioavailability means malaria still places enormous pressure on health globally. It has been found that the solubility of highly lipophilic compounds can be enhanced through lipid formulations, e.g., self-emulsifying drug delivery systems (SEDDSs). Thus, quality-by-design and characterization were used to justify the development and determine the feasibility of oral oil-in-water SEDDSs comprising a fixed-dose combination (FDC) of artemether–lumefantrine to treat malaria more effectively without the aid of a fatty meal. These formulations were compared to a commercial product containing the same active compounds. **Methods:** Excipient compatibility and spontaneous emulsification capacity of different FDC–excipient combinations were identified by employing isothermal microcalorimetry, solubility, and water titration tests. Pseudoternary phase diagrams were constructed, and checkpoint formulations were selected within the self-emulsification region by reviewing formulation properties essential for optimized drug delivery. SEDDSs capable of enduring phase separation within 24 h were subjected to characterization experiments, i.e., drug concentration determination, cloud point, droplet size, size distribution, self-emulsification time, self-emulsification efficacy, viscosity, zeta potential, and thermodynamic stability analysis. SEDDSs with favorable characteristics were identified in the micro or nano range (SNEDDSs) before being subjected to drug release studies. **Results:** All final formulations depicted enhanced artemether and lumefantrine release compared to the commercial product, which could not release lumefantrine at a quantifiable concentration in this study. The avocado oil (AVO)4:6 and olive oil (OLV)3:7 SNEDDSs overall portrayed the ideal characteristics and depicted the highest percentage of drug release. **Conclusions:** This study offers evidence that SNEDDSs from selected natural oils comprising an artemether–lumefantrine FDC can potentially enhance the bioavailability of these lipophilic drugs.

Keywords: artemether (ART); lumefantrine (LUM); malaria; lipophilic drugs; lipid-based dosage forms; self-emulsifying drug delivery systems (SEDDSs); self-nanoemulsifying drug delivery systems (SNEDDSs); pseudoternary phase diagrams

1. Introduction

Despite rigorous attempts to control malaria and eradicate it by 2030, it remains an acute febrile infectious disease that is distressing, widespread, and extremely complex, placing enormous pressure on health worldwide [1–6]. This established vector-transmitted disease is endemic to 97 regions and has shown an unfortunate increase in various countries such as South Africa. According to the World Health Organization (WHO), 247 million occurrences of malaria were recounted in 2021 worldwide. Of these incidents, more than 620,000 individuals died, while the WHO African Region represented approximately 96% of all malaria fatalities. Globally, the mortality rate fluctuates between 0.3 and 2.2%, while regions with tropical climates illustrate mortality figures between 11 and 30% [3,7,8]. Unfortunately, it seems that these figures are rising annually despite current interventions. Daniel Vasella, the Chief Executive of Novartis, detailed in 2006 that: “The fight against malaria is a complex one. Availability of the drug is only one element” [9]. However, currently,

drug availability is not the main concern anymore as various diverse methods of infection are being observed. A specific malaria infection process has been documented as ‘Odyssean’, ‘minibus’, or ‘baggage’ malaria. This method grants transference of the *Plasmodium falciparum* parasite, particularly to non-endemic regions, due to the mosquito’s ability to survive inside the luggage of travelers under favorable climatic conditions [10,11]. In addition, ‘airport malaria’ can occur due to the infectious bite of a tropical anopheline mosquito that has traveled by plane (occasionally also internationally). The probability of this mosquito surviving in a different region is notably high before needing a blood meal, as the hot and humid weather of unlikely areas during summer can favor endurance and breeding. Thus, numerous tourists from developed nations are becoming progressively more prone to contracting or spreading malaria annually. Furthermore, both of these transmission routes are related to the often delayed diagnosis of the patients in question, highlighting the danger of malaria [4,12,13] and identifying the mosquito as one of the world’s deadliest creatures (Fig. 1, Ref. [14]), inflicting more harm



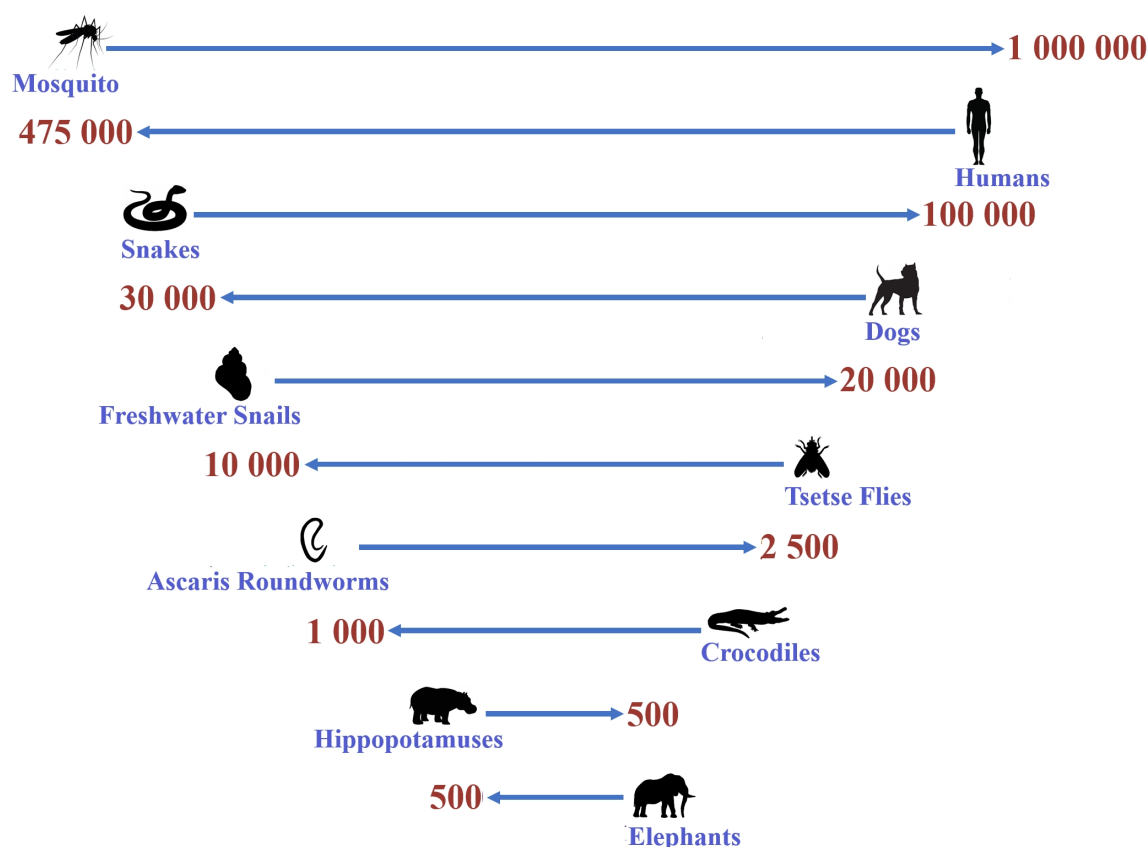


Fig. 1. Illustration of an approximate number of human deaths annually. Adopted from [14].

to humans than most animals [14]. An additional fear is that individuals born in a malaria region develop ‘semi-immunity’ against this parasite owing to enduring various contracted malaria infections; however, when traveling to a non-malaria district, this ‘semi-immunity’ vanishes within 3–6 months, making them just as susceptible to being afflicted by malaria as other individuals [15]. Additionally, the progress of parasitic resistance by *P. falciparum* and *P. vivax* to antimalarial drugs furthermore poses one of the greatest dangers to malaria control and has resulted in increased malaria morbidity and mortality [16,17]. However, it appears that developing drug resistance is not the fundamental distress; it is rather the ‘under-dosing’ of therapeutics that is a significant concern [4,18].

The inability to successfully deliver highly lipophilic therapy to a patient is likely the cause of subtherapeutic drug concentrations achieved during treatment (i.e., erratic and/or inadequate drug absorption) [19–23]. For this reason, studies revealed that a fatty meal is required for more productive treatment when taking antimalarial medication to achieve adequate therapeutic drug concentrations in subjects who are too unwell to eat for the duration necessary to obtain ample improvement [19–23]. This ‘food effect’ is said to enhance the absorption of lipophilic compounds that have been co-administered because of the induction of bile secretion. Sequentially, a solubilizing setting consist-

ing of acid and homogenized fat is provided, and the formed milieu stimulates nutritional lipid absorption [24]. For example, it has been described that oral lumefantrine (LUM) bioavailability can be improved up to 16 times when lipids are provided in conjunction with LUM during treatment [21,25]. In addition, studies showed that lipid amounts as few as two grams can promote adequate quantities of bile salt to increase intraluminal lipid refining and drug solubilization [23]. However, these inferences are problematic. The frequently experienced gastrointestinal disorders associated with malaria, such as nausea, vomiting, abdominal pain, and appetite loss, deter patients from eating adequately—particularly fatty foods [21,26,27]. Subsequently, erratic drug bioavailability, insufficient drug-blood levels for effective treatment as well as patient non-conformity occur [4]. Furthermore, it is extremely challenging for patients living in a low or middle-income country who are not only continuously nauseated but also reside in impoverished regions (most of these regions are tropical) and do not have the resources to obtain appropriate food to eat adequately [28]. It can, therefore, be asserted that under-dosing is likely due to an insufficient drug delivery system that is unable to increase lipophilic drug absorption [4]. Furthermore, the following three considerations should be taken into account when wanting to enhance the effect of antimalarials against the spread of the parasite:

- the active ingredient effect on early gametocyte and non-sexual phases;
- sporontocidal consequences ensue in the mosquito; and
- drug results are achieved on advanced transmissible gametocytes [29].

Treatment of malaria throughout the early phases of the parasite is beneficial because it confidently destroys the parasite during its nonsexual stages. Nevertheless, research should also be conducted on compounds that can eradicate the parasite during the gametocyte phase. For instance, LUM should be considered as it can play a vital role in malaria management [29]. Studies have shown that *P. falciparum* has developed resistance to various artemisinins, especially when utilized as a monotherapy [30]. Although new chemical entities/drugs/compounds are being developed, lack of funding and constraints in developing time cause delays in new treatments reaching the market. This forced the WHO to reflect on alternate dosage treatments that can resist this endemic disease more constructively [1,3,8,17,31]. One such effort by the WHO is the call for developing and employing oral artemisinin-based combination therapies to fight drug resistance, as these combinations have substantially decreased the malaria mortality rate in recent years. Combination therapy has subsequently developed into an area of importance and is now extensively utilized. Artemether (ART) and LUM are, for example, not newly synthesized composites; nevertheless, these two drugs have been prepared into a fixed-dose drug combination (FDC), the commercially available product, Coartem[®], which contains 20 mg of ART and 120 mg LUM. Moreover, the WHO categorized this combination as the first-line treatment in the fight against uncomplicated *P. falciparum* malaria, as it has demonstrated success in efficacy [17,32–39]. Yet, as rationalized, these compounds are highly lipophilic, and their formulation into an efficient dosage form continues to be challenging. Coartem[®], for example, must be complemented with a fatty meal to allow for more effective solubilization and absorption of this FDC. Furthermore, most of the novel drugs currently being synthesized are similar to ART and LUM; they are highly lipophilic, thereby stressing the dilemma we find ourselves in [40–42]. Consequently, due to poor drug solubility, insufficient bioavailability, and often the short half-life of some of the antimalarial drugs, researchers have been driven to focus on drug delivery systems that can advance the therapeutic effectiveness of these drug types [2,4,18–21,29,36,40–48].

Amid the various economically viable technologies that have been researched and proven to enhance drug solubility, address bioavailability difficulties, and improve patient compliance, lipid formulations have been significantly utilized in recognized oral drug products since about 70% of recently discovered drugs and around 40% of commercially available oral drugs are practically insoluble [4,47,48]. One such example is self-emulsifying drug delivery systems

(SEDDSs). Researchers have proposed that there are several mechanisms through which SEDDSs can improve hydrophobic drug bioavailability, including the following:

- the fluidity of membranes is increased, which subsequently enables transcellular drug absorption;
- tight junctions between cells are opened, permitting paracellular transport;
- P-glycoprotein-mediated drug efflux and/or metabolism is/are constrained due to gut membrane-bound CYP450 enzymes;
- lymphatic transport together with lipoprotein/chylomicron production stimulation are enhanced;
- *in vivo* dispersion using supplementary surfactants is accelerated; and
- constituent lipids are metabolized, for example [4,23,24,49,50].

However, SEDDSs are a broad expression for certain lipid-based drug delivery systems that should rather be separated into three classes concerning droplet size. Characteristic SEDDSs that form cloudy emulsions with a droplet size of more than 300 nm are called SEDDSs. The second class is self-microemulsifying drug delivery systems (SMEDDSs), followed by self-nanoemulsifying drug delivery systems (SNEDDSs), which are both deemed translucent and possess a droplet size range of 100–250 nm and smaller than 100 nm, respectively. Furthermore, these three classes vary in composition: SEDDSs generally have an oil percentage between 40 and 80% and are prepared by including hydrophobic surfactants with hydrophilic–lipophilic balance (HLB) values lower than 12. SNEDDSs and SMEDDSs generally comprise an oil component lower than 20%. These systems are created by including hydrophilic surfactants with HLB values of >12. Additionally, for SNEDDSs to form, the surfactant and oil parts should first be mixed; water should be added after this step. Conversely, when formulating SMEDDSs, the sequence in which ingredients are mixed is not critical [50–54]. The simplicity of developing these systems through the spontaneous emulsification approach is fascinating due to the basic production method and the unlimited upscaling potential [55].

Presently, no antimalarial FDC has been developed into specific oral hydrophobic drug delivery systems, including SEDDSs, SMEDDSs, or SNEDDSs. Therefore, for the reasons mentioned, this exploratory research aimed to establish oral oil-in-water (o/w) SEDDSs or SNEDDS formulations containing an ART/LUM FDC that comprises certain natural oils to effectively treat malaria by enhancing the solubility of the included drugs and subsequently, meaningfully improve their pharmaceutical availability without the aid of a fatty meal. The natural oils included were selected on their safety profile for oral use, their relative accessibility, and their probability of improving the solubilization of both ART and LUM. Not only was it attempted to improve the solubilization of this highly lipophilic FDC sig-

nificantly, but also to improve the erratic release, dissolution, and subsequent absorption [56] of a commercial product that normally requires consuming a fatty meal during the treatment regime [19,31,57]. However, the effectiveness of a lipid formulation to form a robust self-dispersible SEDDS or SNEDDS is typically incident-explicit; therefore, the composition of a SEDDS or SNEDDS formulation should be determined [50,58–60]. Consequently, this study employed a valuable assessment tool, namely, pseudoternary phase diagrams, to evaluate the effect of the tested formulation constituents on the *in vitro* performance of the formulations. This tool offers a scientific basis to decide which excipients and in what concentrations they should be included during formulation [61]. To facilitate the reading of this paper, the authors used the term ‘SEDDSs’ to collectively refer to both SEDDSs and SNEDDSs until a distinction between the obtained formulations could be made. Chosen natural oils (peanut: PNT; olive: OLV; coconut: CCT; castor: CAS; and avocado: AVO oil), surfactants (sodium lauryl sulfate and Tween®80), and co-surfactants (Span®60 and Span®80) were utilized to facilitate proper formulation. The formed SEDDSs were compared to a commercial product containing the same active compounds in approximately the same amounts.

2. Materials and Methods

2.1 Materials

ART was donated by DB FINE CHEMICALS (Pty) Ltd. LUM was offered by Cipla Pty Ltd. (Mumbai, India). Peanut (PNT), olive (OLV), coconut (CCT), castor (CAS), and avocado (AVO) oil were acquired from Scatters Oils (Johannesburg, South Africa). Sodium lauryl sulfate (SLS) was secured from Merck Chemicals (Pty) Ltd. (Johannesburg, South Africa); Tween®80 was purchased from Associated Chemical Enterprises (Pty) Ltd. (Johannesburg, South Africa); Span®60 was obtained from Sigma-Aldrich Chemistry GmbH (Steinheim, Germany); and Span®80 was acquired from Industrial Analytical (Pty) Ltd. (Johannesburg, South Africa). The distilled water was obtained using a Reophile Bioscience Ltd. system (Boston, MA, USA), and all other analytes utilized were of analytical grade.

2.2 Preformulation Studies

2.2.1 Infrared (IR) Spectroscopy

IR was employed to identify the donated ART and LUM samples and verify that these powders contained no impurities. The positions of the absorbance bands at different wavelengths of the received ART and LUM batches were individually compared to the positions of the absorbance bands of the known, pure reference standards. An Alpha sample compartment RT-DLaTGS IR (ATR) spectrometer (Bruker, Billerica, MA, USA) was used, and analysis was conducted in the spectral range between 4000 and 400 cm^{-1} with 32 scans and a resolution of 4 cm^{-1} . The ATR unit is delineated with a clamping tool warranting

good contact with the test samples, which, in turn, permits excellent reproducibility. The ATR unit guarantees faster testing with no prior sample preparation, and there is minimal room for operator error [62].

2.2.2 Isothermal Microcalorimetry (IMC)

Excipient compatibility was recognized according to a previously published method [63,64] employing a 2277 thermal activity monitor, TAMIII (TA Instruments, New Castle, DE, USA) furnished with an oil bath (stability: $\pm 100 \mu\text{K}$ during 24 h). The set temperature was retained at 50 °C, during which the samples (100 mg) were analyzed. Heat flow was measured for all distinct components to attain a theoretical response (i.e., baseline). Subsequently, the theoretical response was correlated to the measured calorimetric output to conclude compatibility. Interactions between the tested excipients were only possible if the theoretical response varied exceptionally from the measured calorimetric output. If the heat flow changed during testing with more than 100 $\mu\text{W/g}$ (interaction error), with extra sloping noted, probable incompatibility was denoted.

2.2.3 Solubility

An excess amount ($\pm 500 \text{ mg}$) of either ART or LUM was supplemented with 5 mL of each oil tested in a screw-capped cylinder and vortexed for 2 min, enabling a uniform dispersion. Subsequently, each sample was agitated in a water bath ($37 \pm 0.5 \text{ }^\circ\text{C}$) for 48 h, then centrifuged (3000 rpm) at 25 °C for 15 min. The supernatant (1 mL) was removed and diluted to 20 mL with tetrahydrofuran (THF).

Samples were analyzed employing an Agilent® 1100 high performance liquid chromatography (HPLC) system (Agilent Technologies, Palo Alto, CA, USA) at $30 \pm 0.5 \text{ }^\circ\text{C}$, equipped with a Luna C₁₈-2, $150 \times 4.6 \text{ mm}$, 5 μm column (Phenomenex, Torrance, CA, USA) and furnished with an Agilent® 1100 pump, UV-detector, as well as an autosampler injection mechanism. The mobile phase consisted of acetonitrile (85% v/v) and octane-sulphonic acid (15% v/v) at pH 3.5, with a flow rate of 1 mL/min and detection wavelengths of 210 nm and 303 nm for ART and LUM, respectively. Each formulation was tested in triplicate (i.e., $n = 3$). Chemstation Rev. A10.02 software (Agilent Technologies, Palo Alto, CA, USA) was installed for data collection [63,65].

2.2.4 Pseudoternary Phase Diagrams

Pseudoternary phase diagrams of the drugs, oils, surfactant phase (surfactant and co-surfactant), and water are valuable in concluding the most suitable combination of excipients to form effective SEDDSs. When combined, these illustrations recognize the self-emulsifying areas and verify the ideal concentrations and fractions of the aforementioned components [63,66,67].

Pseudoternary phase diagrams of the selected oils included were created employing the water titration method

[58,59,63,68]. The surfactant phase was set at a 1:1 concentration fraction as the literature resolved it to produce more stable SEDDSs. Higher fractions expand the emulsion range; however, these ratios aid a decrease in stability that might trigger the precipitation of included drugs [66,67]. ART and LUM concentrations (% w/w) differed according to their individual solubility in a selected oil [69]. The surfactant phase and the chosen oils were primed in set fractions (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9), during which water (varying element) was supplemented dropwise at $\pm 25^\circ\text{C}$ until the first indication of milkiness that served as identification of the endpoint. Subsequently, all endpoints were drawn using Triplot software (version 4.1.2, Informer Technologies, Inc.; Asheville, NC, USA), to create pseudoternary phase diagrams that deduced the spontaneous emulsification zone for each tested oil [63].

2.2.5 Visual Appearance

All formulations were visually examined for transparency and optical isotropicity. Each microscopic appearance of a SEDDS was observed using cross-polarized light microscopy (Nikon® Optiphot PFX microscope, Bangkok, Thailand). The system is classed as in the microemulsion array if the detected solution is black. However, droplet size was confirmed using a Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK) [58,59,61,68,70].

2.3 Formulation of Self-Emulsifying Drug Delivery Systems (SEDDSs)

Selected SEDDS formulations were prepared utilizing aqueous phase titration and using the results from the erected pseudoternary phase diagrams. The ART/LUM FDC was dispersed in each selected oil and exposed to sonication for 2 min with a UP400St (400 W, 24 kHz) Hielscher's digital ultrasonic device (Hielscher Ultrasonics, Teltow, Germany). A chosen surfactant phase was separately organized through constant stirring and heating for 25 min. Then, each oil phase was added to the surfactant phase according to the ratios determined while incessantly stirring for an extra 25 min. Small additions (less than 5% w/w) of deionized water were subsequently included with lag times in between until the predetermined amount was incorporated. Before storage at room temperature ($25 \pm 0.5^\circ\text{C}$) for 24 h, each SEDDS was left to cool. The SEDDSs were visually inspected to establish any phase separation or to identify any other instability [61,63,71–74].

2.4 Characterization of Self-Emulsifying Drug Delivery System (SEDDS) Formulations

2.4.1 Assay

A 5 mL SEDDS sample from each batch was filtered through a $0.45\ \mu\text{m}$ membrane filter. Each deposit was first diluted with THF and then further diluted with methanol to attain a final volume of 10 mL. These samples were positioned in HPLC vials and analyzed in triplicate using HPLC, as detailed in Section 2.2.3.

2.4.2 Droplet Size, Size Distribution, and Zeta Potential

Mean droplet size, zeta potential, and size distribution were evaluated using dynamic light scattering conducted at 25°C by a Zetasizer Nano® ZS (Malvern® Instruments Ltd., Worcestershire, UK).

2.4.3 Efficacy and Self-Emulsification Time

A 1 mL sample of each SEDDS was added to 100 mL of distilled water, maintained at 37°C ($\pm 0.5^\circ\text{C}$) in a type II Distek 2500 dissolution system apparatus (Distek, North Brunswick, NJ, USA). These samples were gently agitated at a blade speed of 50 rpm. The time needed to form a clear homogeneous dispersion by an individual SEDDS was monitored, and the spontaneous emulsification effectiveness was classified as corresponding to Table 1 [58,75].

2.4.4 Viscosity

A Brookfield® Viscometer model DV-II+ (Brookfield Engineering Laboratories, Inc., Stoughton, MA, USA), fastened to a flowing water bath and furnished with a Brookfield® temperature device, was utilized. The heat of the water sleeve was preserved at 25°C ($\pm 0.5^\circ\text{C}$) [76]. An SC4-34 LV spindle and Helipath were selected to guarantee optimal torque, which depended on the thickness of the SEDDSs. Every 10 sec for 5 min, viscosity values were noted at 20 rpm, where rotating force values of approximately 20% were conserved. The average of 32 readings was calculated and presented.

2.4.5 Cloud Point

Each fixed-dose SEDDS combination was diluted (1:100) with purified water, and the sample was initially positioned in a water bath at 25°C . Progressively, the temperature was increased at $2^\circ\text{C}/\text{min}$ until an opaque presence (i.e., the cloud point) of the tested formulation was depicted, indicating dehydration of the included excipients [77,78].

2.4.6 Thermodynamic Stability Analysis

The formulated SEDDSs were subjected to fluctuating temperatures (freeze-thaw sequences) during three sequences of about 4°C and 45°C , not surpassing 48 h. Each SEDDS was accordingly inspected for potential phase separation or drug precipitation. Following, these formulations were centrifuged at 3500 rpm for 30 min; whereafter, they were again evaluated for any signs of instability, for example, cracking, creaming, and/or phase separation [79]. Lastly, SEDDS formulations were diluted 100 times using distilled water. Each sample was retained at 25°C for 24 h preceding visual assessment for drug precipitation and/or phase separation [59].

2.5 Drug Release Experiments

2.5.1 Dissolution Behavior

The effect of exposing SEDDSs to both gastric and intestinal pH levels upon drug release was controlled in pro-

Table 1. Rating method for self-emulsifying drug delivery systems (SEDDS) emulsification behavior after dilution.

Grading	Description
Grade A	Immediate emulsion formation, exhibiting a clear/bluish emergence within 60 sec
Grade B	Instant bluish emulsion establishment within 60 sec
Grade C	Delicate milky emulsion that formed within 120 sec
Grade D	Cloudy, greyish to white emulsion that depicts a vaguely oily presence, and which is slow to cream (prolonged: >120 sec)
Grade E	Defective or negligible emulsification seen. Sizable oil droplets detected on the emulsion surface

gressive dissolution settings (100 rpm stirring rate; regulated temperature: 37 ± 0.5 °C) in a Distek® dissolution system (model 2500, Distek® Inc., North Brunswick, NJ, USA) using biorelevant media. The system was attached to a Distek® Evolution 4300 auto sampling unit (model 4301920) and a Distek® syringe pump (SP02716) according to the BP basket technique [80]. This experiment was run for 12 h, and each SEDDS was tested six times ($n = 6$). The successive procedure was as follows: 600 mL initial solution (pH 1.2) sustained for 2 h; followed by adding 300 mL, 0.2 M Na_3PO_4 buffer to establish a pH of 6.8 for 3 h; and lastly, bile salts (3 mM sodium taurocholate, and 7.5 mg sodium chloride) (Merck, South Africa) were included to simulate the fasted state in the intestinal fluid after 300 min at a pH of 7.4 for 7 h [81–83]. At predetermined intermissions (2, 5, 10, 20, 30, 60, 90, 120, 150, 180, 240, 300, 390, 480, 600, and 720 min, as well as an infinite sample at 150 rpm after 750 min), the samples were withdrawn, filtered (45 μm filter), and evaluated with HPLC.

2.5.2 Analysis of the Drug Release Mechanism

DDSolver software (freely accessible menu-driven add-on program for Microsoft® Excel™ 2016 for Windows™; Microsoft® Corporation, Seattle, Washington, USA) was employed to assess altered ART and LUM release patterns through mathematical representations [84]. The release kinetics of both ART and LUM were appropriated with DDSolver for all the representations of the program. Lag-time-release characteristics were further examined. The DDSolver program presents several statistical theories to analyze the goodness of fit of a model. However, for the release kinetics of ART and LUM evaluated in this study, as well as to recognize the best-appropriated model and the mechanical credibility of the model, the correlation coefficient (r^2) and the model selection criterion (MSC) were employed [84,85]. Moreover, the release exponent (n) was interrelated to narrate the mechanism of drug release, that is, Case II transport, Super Case II transport, Fickian diffusion, or non-Fickian diffusion. The concerned reader is referred to Zhang *et al.* [84] for a complete perception of the aforementioned selection principles.

2.6 Statistical Data Analysis

For this study, the fit factors and mean dissolution time (MDT) [86] were calculated, followed by the construction

of the release profiles. Subsequently, the dissolution profiles of all SEDDSs and the commercial product (the control) were related and reflected according to the individual MDTs and fit factor results. Moreover, the fit factors for the correlating formulations are offered in the Supplementary Material (**Supplementary Tables 1,2**). MDT indicates the mean time interval for an entire drug dose to be emitted from a dosage form into a solution (Eqn. 1).

$$MDT = \frac{\sum_{j=1}^n t_{mid} \Delta x_d}{\sum_{j=1}^n \Delta x_d} \quad (1)$$

where n is the total number of samples; j is the sample number; t_{mid} represents the midpoint time between j and $j - 1$; Δx_d signifies the surplus mass of drug dissolved between j and $j - 1$.

The fit factor, f_1 , is the difference factor (Eqn. 2) that defines the percentage error between two curves. Curves deemed identical are characterized by a zero value. Ideally, the f_1 value should be equal to or less than 15 because this implies that the time taken to disperse the drug relates to both the control and sample formulations. Fit factor, f_2 (Eqn. 3), is the similarity factor between two graphs and is a logarithmic conversion of the sum of squares error. A value equal to or higher than 50 signifies that the control and sample formulations are comparable. A value of 100 demonstrates that the two samples are alike [85,87].

$$f_1 = \frac{\sum_{j=1}^n |R_J - T_J|}{\sum_{j=1}^n (R_J + T_J) / 2} \times 100 \quad (2)$$

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{j=1}^n |R_J - T_J|^2 \right]^{-0.5} \times 100 \right\} \quad (3)$$

where R_J is the reference test at time, t . T_J is the test result at time, t , and n is the number of tug points.

Statistica software (ver.12; TIBCO Software Inc., New York, NY, USA) was utilized to perform a one-way analysis of variance (ANOVA) where p -values ≤ 0.05 were considered statistically significant.

Table 2. Average interaction heat flow data obtained for the different component combinations tested in a 1:1:1:1:1 (ART:LUM:oil:surfactant 1:surfactant 2) ratio. The interaction error for each combination is given in brackets ($\mu\text{W/g}$).

ART/LUM FDC with Specified Surfactants	Average heat flow ($\mu\text{W/g}$)				
	Avocado oil	Castor oil	Coconut oil	Olive oil	Peanut oil
Tween [®] 80 + Span [®] 60	4.78 (4.15)	4.92 (9.93)	12.67 (12.78)	5.377 (6.55)	0.70 (0.01)
Tween [®] 80 + Span [®] 80	9.58 (3.85)	9.70 (11.4)	11.99 (12.40)	1.15 (1.49)	16.91 (17.31)
Sodium lauryl Sulfate + Span [®] 60	14.12 (1.42)	20.58 (27.06)	15.32 (16.60)	24.75 (21.52)	21.57 (24.54)
Sodium lauryl sulfate + Span [®] 80	19.91 (19.52)	1.29 (4.02)	5.44 (6.42)	7.12 (6.58)	8.77 (9.34)

ART, artemether; LUM, lumefantrine; FDC, fixed-dose combination.

3. Results and Discussion

3.1 Preformulation and Characterization Studies

3.1.1 Infrared (IR) Spectroscopy

IR spectroscopy is a trustworthy procedure to detect and verify different samples by comparing their unique wavelengths, intensities, number of bands present, and band contours [88]. The IR spectra of standard ART and LUM references and those of donated ART and LUM batches were individually measured. The resulting IR spectra were compared through data overlays of the spectra (**Supplementary Material, Supplementary Figs. 1,2**). Both active ingredients were identified and verified to be pure compounds without contamination since the peaks and intensities of the samples correlated with those of the individual reference standards. Moreover, the absence of additional peaks at different intensities ruled out the presence of any contaminants.

3.1.2 Isothermal Microcalorimetry (IMC)

IMC is a highly sensitive and useful instrument for studying thermal activities by measuring heat flow and temperature fluctuations ($\pm 0.1 \mu\text{W}$). With IMC, it is possible to establish, for example, chemical degradation, crystallization, and composite interactions [63,89,90].

Table 2 shows that no incompatibilities could be identified for any tested oil, drug, and/or surfactant combination. Likewise, no significant differences in heat flow or additional sloping were noticed (**Supplementary Material, Supplementary Figs. 3–7**), which may be ideal for formulating SEDDSs containing an ART/LUM FDC. Overall, combinations comprising either OLV or CAS depicted slightly less heat flow during testing, whereas combinations that included AVO displayed heat flow values that were marginally higher, comparatively. Nonetheless, no trough or slope was observed in the interaction curves, meaning no incompatibilities could be detected, thereby deeming all the selected mixtures unanimous (**Supplementary Material, Supplementary Figs. 3–7**). Therefore, all excipients could be further utilized in this study.

3.1.3 Solubility

The failure of highly lipophilic drug treatment, such as ART and LUM, has been associated with incomplete ab-

sorption of active ingredients due to poor aqueous solubility [20,45]. For this reason, the key challenge remains to construct a delivery system that can effectively enhance the solubility of both drugs. Christian *et al.* [91] proposed that the stability and solubility of these compounds could be improved in the presence of oils or lipids. SEDDSs improve drug absorption by distributing the drug in a dissolved state, thus evading the conventional drug dissolution action. Furthermore, drugs can remain solubilized during preparation, dispersion, and digestion [92,93]. The existence of lipids or lipid-based formulations in the duodenum acts on the principle that the presence of exogenous lipids will cause the creation of colloids into which the active ingredients can divide (i.e., into which the drugs can partition, solubilize, and in turn, enhance absorption), thereby increasing their solubilization within the microenvironment and affording a concentration increase for lipid absorption [93]. Furthermore, due to their microscopic droplet size, emulsified drugs are straightforwardly absorbed by the lymphatic system, thus avoiding hepatic first-pass metabolism. In general, by increasing drug solubilization through the formulation of SEDDSs, absorption over the intestinal epithelial tissue is also substantially increased for BCS Class II drug molecules [92,94–96]. According to the BCS, ART and LUM are categorized as Class II drugs, indicating that both active compounds are very sparingly soluble [97,98], and when solubilizing these drugs in any of the selected oils, their solubility will increase significantly, which, in turn, will enhance absorption and subsequent bioavailability.

Generally, ART showed noticeably higher solubility in the selected oils than LUM (Table 3). The solubility of the drugs in CCT is considered the highest comparatively. Even so, the solubility of both drugs was markedly higher in all of the assessed lipophilic agents, and the subsequent rank order regarding lipophilic vehicle solubility may be reflected as CCT >> AVO >> OLV $\geq$ PNT >>> CAS. Here, CAS comprises a dominant fatty acid (90%), ricinoleic acid ($\text{C}_{18:1}$), which is a uniquely hydroxylated, monounsaturated, 18-carbon aliphatic monobasic acid with a terminal carboxyl group, and a branch-out hydroxyl group whose twelfth carbon is asymmetrical. The bulk of the triacylglyceride molecules found in CAS contain three ricinoleic acid molecules associated with a glycerol moiety [99]. These groups can enhance the solubility of com-

pounds if the solutes possess good hydrogen donors and accepting properties. ART and LUM, however, illustrate meager hydrogen donor and acceptor characteristics, which may be the reason for their poor solubility in the CAS compared to the other oils. However, their solubility still increased exponentially when introduced to CAS [100,101].

Table 3. Solubility (mg/mL) of ART and LUM was determined in the selected oils used in this study.

Vehicle	Solubility (mg/mL)*	
	ART	LUM
Avocado oil (AVO)	127 ± 1.000	1.00 ± 0.000
Castor oil (CAS)	74 ± 1.000	0.70 ± 0.064
Coconut oil (CCT)	135 ± 0.577	2.00 ± 0.000
Olive oil (OLV)	118 ± 0.577	1.00 ± 0.057
Peanut oil (PNT)	113 ± 0.577	1.00 ± 0.057
Water	2.00 ± 0.260	0.13 ± 0.015

*Data are presented as the mean ± standard deviation.

3.1.4 Pseudoternary Phase Diagrams and Visual Appearance

Among the many tools available to advance the solubility of highly lipophilic compounds and surpass bioavailability concerns, economically sustainable lipid formulations, such as SEDDSs, have been highly retained in several recognized oral drug products [4,47,48]. SEDDSs are uniform mixtures of active compound(s) with a blend of lipids, surfactants, and co-surfactants able to generate spontaneous thermodynamically stable oil-in-water dispersions (emulsions) [102]. This pharmaceutical technology has become a promising strategy for developing improved oral drug delivery systems incorporating active pharmaceutical ingredients with notably low aqueous solubility features (i.e., biopharmaceutical classification system (BCS) Class II drugs). The ability of these systems to yield emulsions post-exposure to modest agitation and dilution through the addition of a water phase offers an uncomplicated process for advancing lipophilic drug delivery, where continued drug dissolution in the aqueous environment of the gastrointestinal tract is termed the rate-limiting phase, which influences drug absorption [49,55]. Moreover, SEDDSs can significantly improve drug bioavailability as these systems have been reported capable of circumventing the dissolution phase after oral administration, and they may even evade first-pass metabolism. Moreover, SEDDSs, and more specifically, SNEDDSs, have become a promising tactic permitting the advancement in oral drug delivery system development that contain active compounds with remarkably poor aqueous solubility as it has been found that these systems can improve the bioavailability of such drugs. What is more, and as stated previously, lipid amounts as little as two grams are required to effectively solubilize lipophilic compounds [21,26,27], thus demonstrating that

SEDDSs and/or SNEDDSs will be capable of enabling increased antimalarial drug solubilization and absorption when a fatty meal is highly unlikely or impossible for a patient to take during treatment due to economically straining circumstances [43,55,102].

However, spontaneous emulsification is specifically governed by the selection of excipients that complement each other to form a vehicle designed to improve drug delivery [55,63,103,104]. Self-emulsification will only be accomplished if the additives are well-suited and competent to prompt spontaneous emulsification when subjected to mild agitation. Therefore, a careful selection of excipients is vital. Self-emulsification has been shown to depend on the nominated lipid/surfactant blend, the concentration of surfactant, and the ratio of lipid to surfactant included in the formulation [105]. Research has also established that only certain additive mixtures can induce the configuration of unprompted emulsions [52,55,105]. For this reason, pseudoternary phase diagrams, which are a systematic development approach, are frequently utilized to aid in establishing the most appropriate composition of compounds to formulate SEDDSs. Pseudoternary phase diagrams classify the self-emulsifying regions and conclude the ideal concentrations and proportions of oil, surfactant, and co-surfactant when combined. When the area of a SEDDS is determined, the viability of producing an emulsion can be established [58,59,106]. Construction of these diagrams enables a schematic depiction of the zone of self-emulsification when specific excipients are used in a mixture [106,107]. Pseudoternary phase diagrams are practical tools that can project the phase behavior of a potential SEDDS or SNEDDS, as different regions of the illustration expose different behavioral properties of emulsions. For example, they can explain the strength of dilution of a SEDDS or SNEDDS in the gastrointestinal milieu [55,106].

As stated, the purpose of this study was to formulate stable, o/w nanoemulsions, which include natural oils that can be utilized for oral lipophilic drug delivery. Fig. 2 represents the pseudoternary phase diagrams created after testing the different combinations of selected excipients deemed feasible to formulate for oral drug delivery. The pseudoternary phase diagrams that indicated unstable SEDDS formulations can be viewed in the **Supplementary Material (Supplementary Figs. 8,9)**.

All SEDDSs containing sodium lauryl sulfate (SLS) as the surfactant were omitted from further analysis because these systems produced either a narrow range to experiment with or unstable spontaneously formed emulsions. SLS was initially chosen as a surfactant due to its significant hydrophilicity (HLB value = 40) and ability to form o/w emulsions [60]. However, the oils tested possess HLB values between 6 and 12, making them notably more lipophilic [108]. Generally, the HLB system is a simple scientific method for forecasting the optimal surfactant/co-surfactant combination needed to create an ideal emulsifying system. An

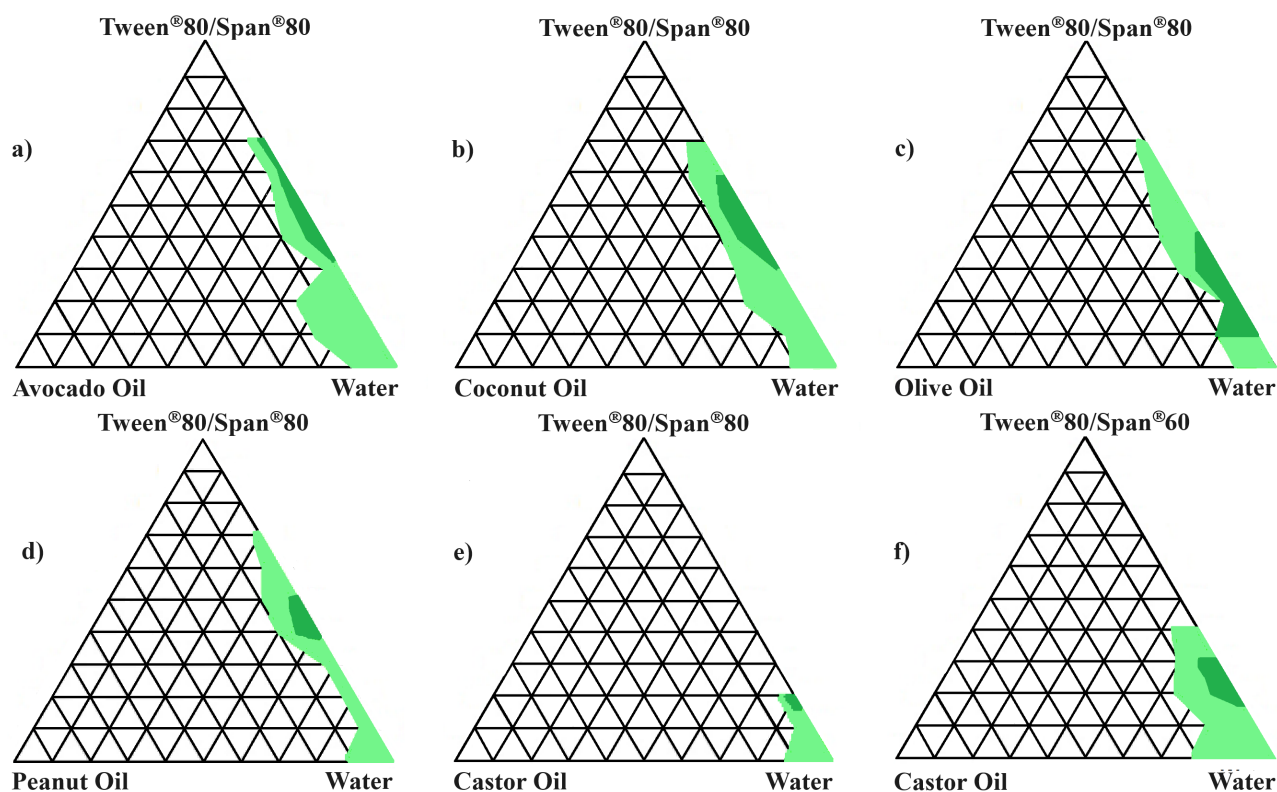


Fig. 2. Pseudoternary phase diagrams. (a) Avocado oil, ART/LUM, Tween[®]80/Span[®]80, and water. (b) Coconut oil, ART/LUM, Tween[®]80/Span[®]80, and water. (c) Olive oil, ART/LUM, Tween[®]80/Span[®]80, and water. (d) Peanut oil, ART/LUM, Tween[®]80/Span[®]80, and water. (e) Castor oil, ART/LUM, Tween[®]80/Span[®]80, and water. (f) Castor oil, ART/LUM, Tween[®]80/Span[®]60, and water. The uncolored region denotes the coarse dispersion region, whereas the green part signifies the single-phase emulsion area, where the light green zone specifies the liquid crystal region, and the dark green section denotes the nanoemulsion area.

optimal and stable emulsifying system is founded when the HLB values of the selected oil and surfactant phases match [61,108–111]. In this case, the unstable formulations obtained are probably due to the HLB values not complementing one another; thus, the hydrophilicity of the components does not correspond.

The remaining SEDDSs were also visually examined as described during the preformulation phase. Optically clear emulsions were deemed acceptable for further analysis (Fig. 3a), whereas SEDDS formulations depicting crystallization, precipitation (Fig. 3b), or other instabilities were disregarded.

Based on the pseudoternary phase diagrams and photographic examination, SEDDSs that adhered to the set principles, and in which the quantity of oil phase entirely solubilized the ART/LUM FDC, were reserved at 25 °C for 24 h to identify any phase separation. All SEDDSs comprising a surfactant phase of Tween[®]80 and Span[®]60 showed phase separation, except for CAS3:7S60. Hence, the remaining SEDDS formulations were deemed appropriate for further characterization testing, as seen in Table 4. Abbreviations were assigned to the combinations tested to

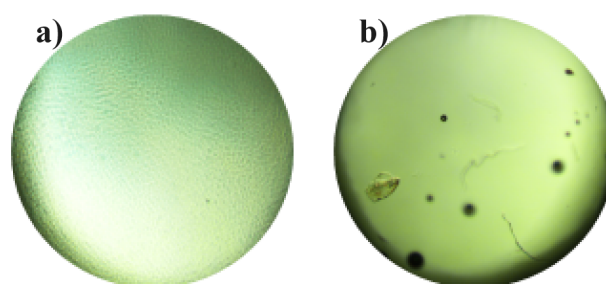


Fig. 3. Microscopic SEDDS examples. (a) Acceptable SEDDS formulation. (b) Undesirable SEDDS that either started to precipitate or form crystals.

aid in-text referencing. The assigned code begins with a three-letter designation indicating the oil type used. This is followed by a ratio representing the aforementioned oil to the surfactant phase. The S60 or S80 indicated for the CAS SEDDSs is to differentiate between the co-surfactant utilized in these formulations.

Table 4. Characterization of SEDDSs that did not pose initial phase separation. Properties that did not meet the set standards for a particular performed test are specified in bold and are highlighted. All experiments were conducted thrice, and only the average values are displayed.

SEDDS	Assay (%)		Droplet size (nm)	Zeta potential (mV)	Self-emulsification grading	Self-emulsification time (s)	Cloud point (°C)	Viscosity (mPa.s)
	ART	LUM						
AVO4:6	105.513	96.553	241.3	−43.8	A	35	62	402.1
CAS2:8S80	95.493	95.200	524.1	−44.6	B	59	55	372.0
CAS3:7S60	96.723	95.735	249.4	−20.8	C	120+	55	312.0
CCT6:4	105.600	96.310	776.2	−46.6	A	55	45	200.0
OLV3:7	107.588	96.000	241.2	−54.7	A	40	60	510.2
PNT6:4	112.375	96.211	1452.7	−45.7	A	50	60	278.8

3.1.5 Assay

The International Pharmacopoeia (IP) affirms that oral dosage forms comprising ART and LUM should have an individual drug concentration between 90% and 110% [112]. From Table 4, it is clear that, in general, ART depicted a higher drug content percentage in SEDDS formulations compared to LUM. Nonetheless, the drug content percentage for both drugs fell well within the set criteria, except for the SEDDS that comprised PNT, i.e., PNT6:4 (112.375% ART). Furthermore, the concentrations of ART and LUM (to a lesser extent) in CAS SEDDSs were notably lower compared to the other SEDDS formulations, regardless of the surfactant included. This is possibly due to the reduced solubility of both ART and LUM in CAS (Table 3). Moreover, no significant ($p \geq 0.05$) differences in the LUM content could be established between the different SEDDSs. Furthermore, the %RSD for ART ranged between 0.431 and 2.580%, whereas the LUM %RSD was between 0.010 and 0.591%, suggesting that all the SEDDSs undoubtedly exhibited a uniform droplet dispersion due to the restricted concentration deviation array for both active compounds.

3.1.6 Droplet Size, Size Distribution, and Zeta Potential

Droplet size, size distribution, and zeta potential mainly influence drug delivery employing SEDDSs [42, 113,114]. Size classification is one of the most perceptive trials carried out during SEDDS development since size affects drug release, SEDDS stability, and absorption [114]. As the droplet size decreases, the available interfacial surface area increases, which sequentially advances abrupt drug release into an aqueous milieu for drug absorption [58,115,116]. Gershanik *et al.* [117] explored the effect of emulsion droplet size on the diffusion capacity of SEDDSs through the intestinal mucosa. They established that the best possible droplet size range is between 100 and 500 nm. AVO4:6, CAS3:7S60, and OLV3:7 SEDDSs each depicted a droplet size smaller than 250 nm, rendering them in the nanosize range and defining these formulations as SNEDDSs (Table 4). Additionally, these SNEDDS formulations depicted a %RSD of <5% in droplet size, indicating a relatively small size distribution, that is, uniform in size.

Consequently, these SNEDDSs were regarded as acceptable for further investigation.

Only PNT6:4 presented an average droplet size in the micro range (1452.667 nm) and a relatively wide droplet size distribution (16.305% RSD). Therefore, PNT6:4 will most probably not be able to diffuse into the intestinal mucosa to the same degree as the SNEDDSs that make up the other oil phases and could also be unstable. Moreover, although the CCT6:4 and CAS2:8S80 formulations fall within the nano size range, they will presumably also not be efficient in traversing the intestinal film to the same limit as the accepted SNEDDSs. The larger average droplet sizes achieved with PNT6:4, CCT6:4, and CAS2:8S80 could be accredited to the oil–surfactant phase fraction. Normally, the droplet sizes enlarged as the oil phase concentration increased and the surfactant phase declined. When droplet size increases, it can lead to flocculation or coalescence of the oil droplets, which, in turn, will probably cause SEDDS instabilities [109]. Thus, these SEDDSs were not deemed acceptable in terms of droplet size and size distribution in this study.

Progressively positive or negative zeta potential values (in other words >30 mV or <-30 mV) denote an increase in electrostatic repulsion between individual droplets and are thus believed to be beneficial as clotting is eluded [118]. However, a small variation is permitted since research found that emulsions stabilized by both steric and joint electrostatic forces (as empowered by Tween® 80) with a minimum zeta potential value of -20 mV can be considered adequate [119,120]. The observed negatively charged zeta potential values (Table 4) are introduced by the free fatty acids present inside the different oils [121]. As demonstrated, all SEDDS formulations, except CAS3:7S60 (still larger than -20 mV), showed zeta potential values greater than -30 mV (i.e., a value higher than 30), which is suggestive of significantly stable SEDDS formulations. It could subsequently be suggested that the co-surfactant type incorporated may again influence the zeta potential obtained. Furthermore, Roland *et al.* [122] concluded that there is no direct association between the general physical stability and the attained zeta potential. They found that emulsions with lower zeta potential values may perhaps only be

branded as more stable once stability experiments are performed. Thus, it could be resolved that zeta potential values that do not differ by more than 10 mV throughout stability testing are necessary to predict absolute emulsion stability. For this reason, all tested SEDDSs complied with the standards set for zeta potential, where, in general, the SNEDDS that consisted of OLV is deemed the most stable.

3.1.7 Efficacy and Self-Emulsification Time

Self-emulsification efficacy may be denoted as dispersibility assessment [123–125]. Instantaneous emulsification is highly promising if detected using SEDDSs aimed at oral administration. This is because spontaneous emulsification is acknowledged as the rate-limiting step that has to transpire before effective absorption [125]. Additionally, when self-emulsification is initiated quickly, it indicates that only a small sum of energy was needed to form the said emulsion; that is, no heating was necessary, for example [58,126,127]. In other words, the self-emulsification time of a SEDDS formulation demonstrates the free energy required to permit self-emulsification that can be induced by the energy-reducing aptitudes of emulsifying agents, which directs the collapse of formulations [128]. The literature established that natural emulsification could transpire immediately or be delayed, subject to the existence of kinetic obstacles between excipients contained in SEDDSs [71]. Furthermore, kinetic barriers can be overcome by applying mild agitation or heat [71], but this should not be required for forming oral SEDDS (mild agitation will be present within the gastrointestinal tract). Thus, given the emulsification behavior grading system for SEDDSs, as demonstrated in Table 1, it could be concluded that SEDDSs, which achieved an A or B grading, could be judged favorable for successful oral delivery of the ART/LUM FDC. However, SEDDSs that showed slow and/or weak emulsification characteristics, with resulting C, D, or E grading, were reasoned inapt.

Hence, CAS3:7S60 (Table 4, highlighted and in bold) was rejected in terms of oral drug delivery owing to an acquired C grading (Table 1). As stated previously, a stable emulsifying system is normally established when the surfactant phase's HLB value, especially when synthetic surfactants are used, is near the HLB value required of the oil phase [61,108–111]. This study calculated the HLB value of the surfactant phase included in CAS3:7S60 as 9.85. CAS, however, has an HLB value of 14, thus indicating a significant difference in HLB values and, therefore, consenting a safe hypothesis to be formed, namely, that the surfactant phase is not effective enough to successfully lower the interfacial tension. The necessary energy to naturally emulsify the formulation consequently favored the diffusion surface area and not the entropy variations of the emulsion.

3.1.8 Viscosity Testing

Viscosity describes the internal resistance of a fluid that can affect flow resistance as well as spontaneous emulsification [129,130]. In general, the lower the viscosity, the faster the rate of emulsification, which, sequentially, may impact the *in vivo* release of a drug and succeeding bioavailability [6,78]. Overall, it was found that viscosity increased as the surfactant phase ratio increased (Table 4). The included natural oils also notably influenced the viscosity but did not influence it to the same extent as the surfactant phase. According to the type of oil incorporated, these obtained viscosity values could be graded as OLV > AVO > CAS > PNT > CCT. Interestingly, no correlation between viscosity and self-emulsification time could be established. Nonetheless, a general trend was noted, whereby the mean droplet size of the SEDDSs that incorporated the same surfactant phase (Tween®80 and Span®80) increased as the viscosity decreased.

All the SEDDSs additionally depicted plastic rheological properties. Most pharmaceutical formulations are manufactured to be pseudoplastic, which makes them advantageous. The justification is that the high viscosity at a lower shear allows for the insoluble particles in the SEDDSs to be stabilized, which then inhibits these particles from promptly sedimenting. Moreover, pseudoplastic flow has a shear-thinning property that grants simple flow when emptying the emulsion container [131]. Consequently, this rheological performance is valuable as it permits the formation of a more stable SEDDS, especially during storage. It furthermore assists with simple use and pouring during administration.

3.1.9 Cloud Point Determination

The cloud point indicates the temperature at which SEDDS formulations cannot maintain their spontaneous emulsification properties [132]. Erratic drug release and irreversible phase separation occur due to dehydration of the incorporated constituents at elevated temperatures above the identified cloud point. These occurrences can harshly influence drug absorption [77,133]. For these reasons, the cloud point for an oral SEDDS ought to be greater than body temperature (i.e., $\pm 37^\circ\text{C}$). As depicted in Table 4, none of the SEDDS formulations tested portrayed excipient dehydration close to body temperature, rendering them suitable for oral drug delivery.

3.1.10 Thermodynamic Stability

The surfactants incorporated into the SEDDS formulations cannot guarantee physical stability due to the intricacy of the emulsified system supported by the included surfactants. These compounds generate interfacial tension slopes and offer adjustment to the mobility of droplets [134]. Therefore, physical SEDDS stability was examined during thermodynamic stability testing [58,63,79].

No physical instabilities were observed when the AVO4:6, CAS2:8S80, CAS3:7S60, and OLV3:7 SNEDDSs were exposed to differing temperatures. Alternatively, the CCT6:4 SEDDS solidified once refrigerated owing to the modest melting point ($\pm 24\text{ }^{\circ}\text{C}$) of CCT. Solidification is, however, not considered a thermodynamic instability. Interestingly, once this formulation was heated to the set test temperature of $45\text{ }^{\circ}\text{C}$, the CCT6:4 SEDDS reverted to its initial liquid state, and no phase separation, cracking, or creaming could be observed, making it a stable formulation. The PNT6:4 SEDDS also depicted solidification during refrigeration, and during the heating cycles, it liquefied, but after the last thermodynamic cycle, visible phase separation emerged, indicating that this formulation was inapt.

The different SEDDSs were then exposed to centrifugation to determine if these formulations could withstand kinetic stress conditions. On visual inspection, no kinetic instabilities were identified, which signified that all tested SEDDSs could be considered acceptable when exposed to the centrifugation experiment. For the last thermodynamic stress test, the selected SEDDSs were diluted to evaluate their robustness, as this simulates comparable circumstances that arise in the gastrointestinal tract upon oral administration [78]. Again, no indication of any physical instabilities of the SEDDSs could be detected.

3.2 Drug Release Experiments

Dissolution Behavior

The dissolution profiles of the commercial product and the SEDDS formulations were related. It was found that ART release from all the SEDDSs differed statistically significantly ($f_1 > 15$; $f_2 < 50$) from the average ART amount released from the commercial product (Fig. 4). This product not only contains ART and LUM but also includes the surfactant, polysorbate 80, as well as filling agents, microcrystalline cellulose and hypromellose. Hypromellose possesses gel matrix forming properties; together with the surfactant, it made interesting conclusions relating to the dissolution release kinetics of ART and the percentage of ART released. Polysorbate 80 could provide adequate moistening of ART at a low pH (1.2), which in turn permitted the earlier detection of ART (MDT = 235.252 min), comparatively. Furthermore, a rise in pH to a value of 6.8 corresponded to a noticeable peak in ART release from this commercial product, expressing that it fit the Peppas–Sahlin 2 with T_{lag} model. This is due to tablet erosion occurring within 2 min from the start of dissolution testing, followed by the ART diffusing from a gel matrix that subsequently arose due to the incorporated hypromellose [81].

In contrast, all the tested SEDDS formulations depicted initial delayed ART release profiles until approximately 120 min, despite being liquid formulations, and this coincided with when the pH of the dissolution medium was changed from 1.2 to 6.8. This is further highlighted by the notably high MDT values (Fig. 4) achieved for the differ-

ent SEDDSs. Furthermore, all SEDDSs portrayed release characteristics dependent on an increase in pH and, to a lesser extent, the presence of biorelevant media at 300 min when pH was again adjusted from 6.8 to 7.4 after adding phospholipids and bile salts. Moreover, SEDDS formulations that included CAS showed a slower onset of drug release, signifying that this oil had the most retardation properties of ART release. However, once ART release was initiated, these SEDDSs were able to release more ART (100%) faster compared to the other SEDDSs ($f_1 > 15$; $f_2 < 50$), denoting that the type of oil phase played a notable part in ART release. Remarkably, it was observed that the higher the surfactant phase included, the more ART was released. The ART release rate could be ranked (slowest to fastest release rate): $\text{OLV3:7} \geq \text{AVO4:6} \gg \text{PNT6:4} > \text{CCT6:4} \gg \text{CAS2:8S80} > \text{CAS3:7S60}$. However, no correlation between release rate and ART amount dissolved could be established. Nonetheless, a quasi-linear ART release was observed for all the SEDDS formulations ($r^2 \geq 0.982$) from the time ART release commenced (120 min). The commercial product tablets ($n = 6$) were only able to obtain an average ART pharmaceutical availability of 86.12%, whereas the SEDDSs, except for CCT6:4 (84.63%), overall presented higher dissolved ART concentrations (average of 97.10%). Yet, all formulations adhered to the established percentage ART release criteria [80].

Considering the fit factors (Supplementary Material, Supplementary Table 1) between the selected SEDDS formulations tested, only the SEDDSs comprising CAS, irrespective of the surfactant phase included, differed statistically significantly from the other SEDDS formulations. A possible explanation for the differences observed in the various ART release profiles may be the noticeable varying ART solubility in the selected oil phases. ART is meaningfully less soluble in CAS, whereas higher and more comparable solubility results were obtained for the other oils. Meager solubility can cause faster drug release from a preparation (CAS MDT values are relatively faster than most other formulations), whereas improved solubility in a dispersed phase can deter a drug from diffusing from the formulation [135].

Regarding the dissolution profiles constructed for LUM from the different formulations (Fig. 5), it is again clear that LUM was released only after the biorelevant medium was added, with a subsequent meaningful increase in the pH to 7.4 (i.e., after 300 min and even slower than ART). Furthermore, LUM could not be quantified for the commercial product tested, and thus, no comparison to the control could be made.

LUM possesses a log P of 9.19 [60] and log D values (distribution coefficient) of 8.9 and 10.1 at pH 6 and 7.4, correspondingly [136]. These values reflect its noticeable affinity for an organic or lipophilic phase, which, in turn, provides a basic explanation for its poor detection during performed dissolution studies when compared to ART.

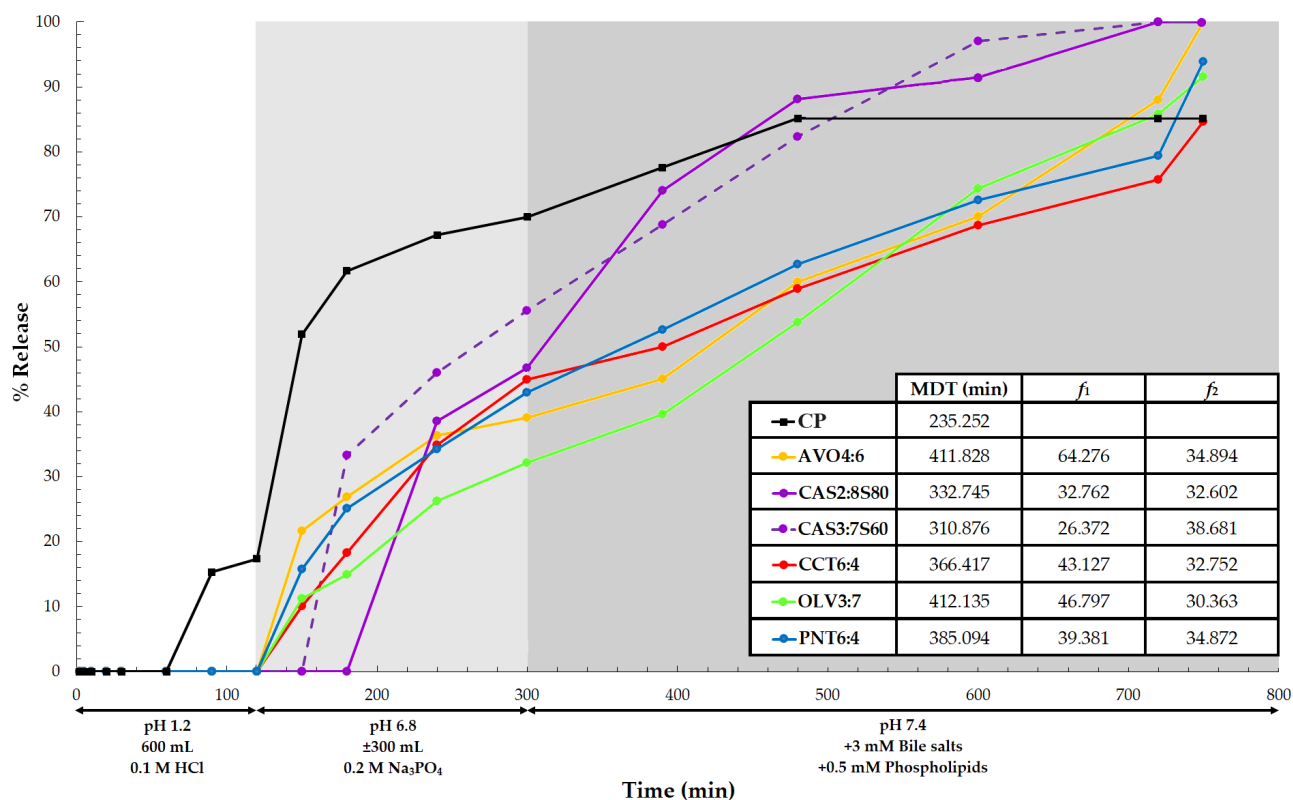


Fig. 4. ART release profiles for the respective SEDDS formulations tested. The shaded areas and interpretations express the time points where changes in the dissolution media were made ($n = 6$). The abbreviation CP indicates the drug release of the commercial product.

However, it could be concluded that the type of phospholipid and its concentration included in the progressive dissolution media were adequate to enhance the wettability of LUM. The increased wettability led to high enough LUM concentrations in the aqueous phase for quantifiable detection when the SEDDS formulations were analyzed. Bile salts and phospholipids are said to implicitly affect the solubility and ensuing bioavailability of poorly soluble compounds owing to bile salts and phospholipids being physiologically significant surfactants. Therefore, the addition of synthetic surfactants to SEDDS formulations appeared to noticeably decrease the interfacial friction between the SEDDS excipients and the immediate fluid [137]. The interfacial tension could subsequently be reduced due to the entropy changes that favor the dispersion because of the combination of surfactants in the dissolution medium.

However, the biorelevant media employed was a simple preferential constitution to imitate the milieu in the small intestine and not to amend or enhance the dissolution of the two drugs utilized. Literature normally suggests the use of two different biorelevant media types when analyzing drug dissolution, that is, Type I and Type II. Type I simulates the fasting state in the gastrointestinal tract, whereas Type II media mimics the fed state. Here, Type I dissolution media was utilized for drug release experiments because

(and as mentioned before) patients contracting malaria normally reside in rural areas; taking a suitable nutritious fatty meal during treatment with the relevant medication is seldom plausible [138]. Thus, it was attempted to establish whether ART and LUM could be released in the fasted state. However, the use of Type I media can be unfavorable in terms of the effective release of highly lipophilic drugs such as LUM during dissolution studies. Comparatively, Type II dissolution media include lecithin, which facilitates lipid digestion, making this dissolution medium more advantageous for the solubilization of lipophilic drugs. Nevertheless, various enzymes are found in the gastrointestinal tract that will normally facilitate lipid digestion and probably improve LUM release from the SEDDS formulations after oral dosing [138]. In addition, there are lipid transport systems in which chylomicrons and micelles aid in carrying the lipids to the absorption region [139]. Therefore, numerous additional mechanisms in the digestive system can contribute to the normally improved bioavailability of LUM *in situ*. Consequently, although the LUM release profiles attained during experimentation show inapt drug release, it could still be considered effective as LUM was sufficiently released for quantification from all the SEDDS formulations (though significantly slowly). Literature additionally stated that LUM displays delayed absorption and elimina-

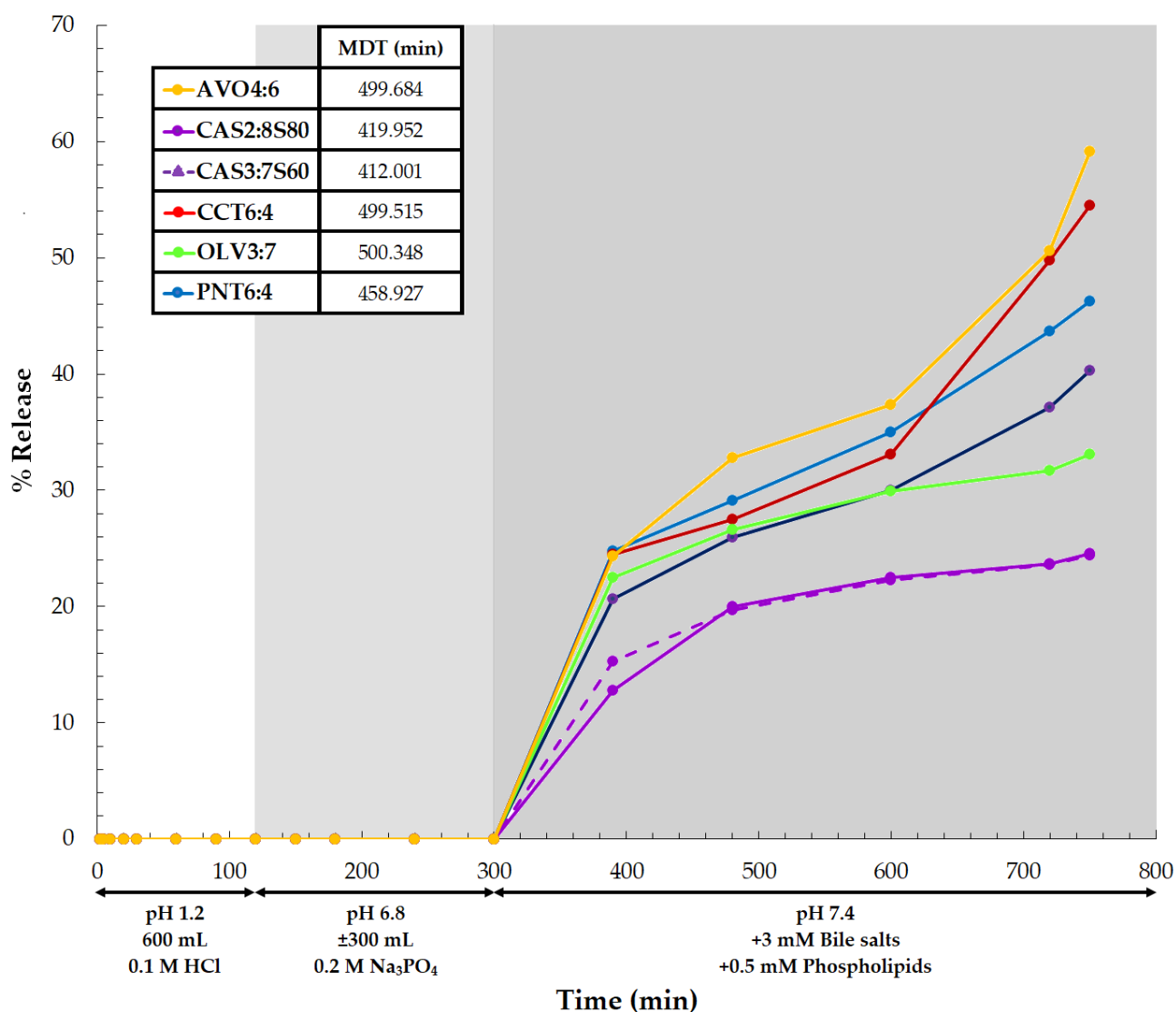


Fig. 5. LUM release profiles for the individual SEDDS formulations analyzed. The colored regions and explanation direct the time points for changes in the dissolution media ($n = 6$).

tion [140]. This property is beneficial as LUM targets the blood schizonticide stage of malaria and presents no anti-malarial activity against the pre-erythrocytic liver stages. Consequently, when taken together with ART, LUM will eliminate all residual parasites once ART has diminished the initial parasites [140,141]. For this reason, having a drug delivery system with delayed LUM release characteristics may aid in treating malaria.

Overall, the LUM concentrations released from the different SEDDSs were significantly lower compared to the ART released from the same formulations. Nonetheless, all the SEDDS formulations again fit the Peppas-Sahlin 2 with T_{lag} model for LUM. The following rating for the cumulative percentage LUM released from the SEDDSs until 750 min could be provided: AVO4:6 (59.1%) > OLV3:7 (54.5%) > PNT6:4 (46.2%) > CCT6:4 (33.1%) > CAS2:8S80 (24.5%) = CAS3:7S60 (24.4%). No sta-

tistically significant differences ($f_1 < 15$; $f_2 > 50$; **Supplementary Material, Supplementary Table 2**) in terms of LUM release, could be established between AVO4:6; CCT6:4; OLV3:7; or PNT6:4. Moreover, CAS2:8S80 and CAS3:7S60 depicted similar delayed LUM release profiles ($f_1 = 3.995$; $f_2 = 96.554$; **Supplementary Material, Supplementary Table 2**); however, the concentration LUM released from these two formulations was significantly lower ($f_1 > 15$; $f_2 < 50$) compared to the other SEDDSs. Furthermore, the LUM release rates from the selected SEDDS formulations followed a trend similar to that of the ART rates, whereby $OLV3:7 \geq AVO4:6 = CCT6:4 \gg PNT6:4 \gg CAS2:8S80 > CAS3:7S60$ (slowest to fastest release rate).

In summary, all tested SEDDSs could release both ART and LUM more effectively than the commercial product. An average lag time (ALT) and MDT of 135 min and

369.849 min, respectively, were shown for when ART was released from the analyzed SEDDSs. These results indicate a faster release rate compared to the release of LUM (ALT = 300 min; MDT = 465.071 min). Moreover, a significantly higher amount of ART (95%) was released relative to LUM (40.3%). No distinct proportional trends could be recognized for the drug concentrations released from the chosen SEDDSs. Both drugs also displayed release kinetics from the different SEDDS formulations that could be related to the Peppas-Sahlin 2 with T_{lag} model. This model accounts for a release profile of a certain compound by matching its release results to either Case II relaxational release or Fickian diffusional release. Fickian diffusion normally indicates solute transport, where the relaxation time of the polymer is larger than the diffusion time of the solvent. Molecular diffusion by the drug from a certain dosage form into the digestive media using a chemical potential gradient initiates Fickian release. When the Fickian diffusion constant (k_1) is higher than 1, it can be presumed that Fickian diffusion occurred. Conversely, Case II relaxational release transpires when a drug is released due to stresses and state transitions inside hydrophilic glassy polymers that expand once in contact with water or biological fluids. Similarly, lipids swell when in contact with the biological liquids [142]. Due to all k_1 values exceeding 1, it could be concluded that Fickian diffusion ensued from the tested SEDDSs (**Supplementary Material, Supplementary Table 3**).

4. Conclusions

Preformulation studies indicated that individual solubilities were exponentially improved by simply dissolving both ART and LUM in the selected natural oils. Moreover, the stability of the six chosen emulsions and nanoemulsion areas depended on the type of surfactant phase incorporated. Except for the SEDDS formulation that included PNT as an oil phase, these emulsions could be classified as SNEDDSs. Additionally, all six formulations exhibited pseudoplastic rheological flow behavior, which is ideal for pharmaceutical preparations, as this type of flow behavior can stabilize any insoluble particles in an emulsion, preventing sedimentation of the said particles [143]. These formulations also exhibited quantifiable ART and LUM release. However, all release profiles indicated that delayed responses for both drugs ensued until the pH of the dissolution fluid was augmented, rendering the drug release pH-dependent. Furthermore, all release profiles of both drugs fit the Peppas-Sahlin 2 with T_{lag} model, highlighting that simple Fickian diffusion occurred when the incorporated drugs were released from the delivery system via a concentration gradient [142,144]. The percentage of ART released from the SEDDS and SNEDDS formulations was significantly higher than the LUM concentrations released. However, these formulations showed improved ART and LUM release compared to the commercial product, which could not release LUM at a quantifiable concentration.

The AVO4:6 and OLV3:7 SNEDDS formulations overall portrayed the most optimum physical SEDDS/SNEDDS characteristics and stability; they depicted the highest percentage of LUM released exhibited exceptional ART release (100% and 91.6%, respectively) and depicted adequate modified drug release. Moreover, dissolution behavior analysis indicated the importance of adding biorelevant media when investigating highly lipophilic active pharmaceutical compounds. Thus, this study offers evidence supporting the credibility of formulating SNEDDSs from selected natural oils that include an ART/LUM FDC to meaningfully enhance the solubility of these antimalarial drugs that frequently fail simply because of varied bioavailability caused by poor aqueous solubility. This, coupled with the validated feasibility of manufacturing SNEDDSs displaying modified drug release properties, could potentially offer uncomplicated *Plasmodium falciparum* malaria treatment with an imperative solution to circumvent treatment failure and subsequent development of drug resistance.

Abbreviations

ANOVA, Analysis of Variance; ART, Artemether; AVO, Avocado Oil; BCS, Biopharmaceutical Classification System; CA, California; CAS, Castor Oil; CCT, Coconut Oil; f_1 , f_2 , Fit Factors; FDC, Fixed-Dose Combination; IMC, Isothermal Microcalorimetry; IP, International Pharmacopoeia; IR, Infrared; k_1 , Fickian Diffusion Constant; LUM, Lumefantrine; MDT, Mean Dissolution Time; MSC, Model Selection Criterion; NJ, New Jersey; o/w, Oil-in-Water; OLV, Olive Oil; PharmacenTM, Centre of excellence for Pharmaceutical Sciences; PNT, Peanut Oil; SEDDSs, Self-Emulsifying Drug Delivery Systems; SLS, Sodium Lauryl Sulfate; SMEDDSs, Self-Microemulsifying Drug Delivery Systems; SNEDDSs, Self-Nanoemulsifying Drug Delivery Systems; THF, Tetrahydrofuran; WHO, World Health Organization.

Availability of Data and Materials

All data and materials used have been included in this paper.

Author Contributions

Conceptualization of the study was done by JMV and LHdP. Methodology was planned and executed by JMV and LC. LC furthermore performed the research/investigation. JMV was responsible for data curation and software. Validation of the study was completed by JMV, LC and LHdP. Following, LC and JMV conducted the formal analysis for this research. Resources were procured by JMV. JMV was responsible for the writing — original draft preparation; and JMV and LHdP were responsible for the writing — review and editing. JMV and LC were in charge of the visualization. Overall supervision and project administration were conducted by JMV and LHdP. Funding

was acquired by JMV. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.fbe1603025>.

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