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FORMULATION AND DEVELOPMENT OF A SELF EMULSIFYING DRUG DELIVERY SYSTEM FOR LUMEFANTRINE

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ABSTRACT

Objective: The objective of the present study was to formulate and development of a novel self-emulsifying drug delivery system to enhance the solubility thereby improving the relative bioavailability of a BCS class II drug Lumefantrine.

Methods: A series of Lumefantrine containing self-nanoemulsifying formulations F1-F9 were prepared using peceol as oil phase, labrasol as surfactant and PEG 400 as cosurfactant, respectively. Lumefantrine was identified by ultraviolet–visible spectroscopy at λmax of 234 nm and FTIR study. All formulation were subjected toinvitro parameters such as dispersibility test, droplet size analysis, viscosity, zeta potential and dissolution study. The optimized formulation F5 was kept for stability studies.

Results: Optimized formulation showed drug release (99.13%) with droplet size (33.84 nm), Zeta potential (-22.2 mV), viscosity (156.2 cP) and infinite dilution capability. *In-vitro* drug release of the was highly significant as compared to pure drug.

Conclusion: The present SEDDS would be a promising novel system to improve the lipophilic drug's dissolution rate and potentially the bioavailability.

Keywords: lipophilic drugs, Solubility, Bioavailability, Self emulsifying drug delivery system, surfactant

INTRODUCTION

SEDDS consist of solid or liquid, synthetic or natural surfactant oils and one or more hydrophilic solvents, as an alternative, of a homogeneous dispersion. Such systems can

produce fine oil-in-water (o / w) emulsions or microemulsions in aqueous fluids following mild agitation. The SEDDS formulations are mechanically stable and simple to produce compared to the metastable dispersion formulations of the emulsions. A large interfacial area for the partitioning of the drug between oil and water is provided by SEDDS formulations, which are an added advantage over simple oil solutions **[1-2]**.

Lumefantrine (LF) is a highly lipophilic derivative of flourene and a Class II Biopharmaceutical Classification System (BCS) drug which is an effective agent for the treatment of falciparum malaria.Lumefantrine is a blood schizonticide, works by inhibiting haem detoxification, causing parasite death by toxic haem and free radicals. It is an effective molecule, but its effectiveness is limited by extremely poor solubility in the aqueous. The solubility is well below the critical requirement for solubility and therefore the recorded bioavailability is 4–11% **[3-4]**. Poor LF oil solubility has restricted lipid-based system growth. Given this inadequacy, the current study aims to improve the Lumefantrine solubility **[3-4]**.

MATERIALS

Lumefantrine was procured from Pravah Lab Pvt., Ltd., Hyderabad, India. The following materials were procured from gattefosse India and were used as received: Capryol PGMC, Labrafil M 2125, Peceol, Labrasol. Tween 80, Propylene glycol, Ethanol, Benzyl alcohol and PEG 400 were purchased from SD Fine Chemicals, Vadodara, India. Coconut oil, Olive oil, and Corn oil were purchased from the local market.

METHODOLOGY

Solubility studies

The solubility of the drug samples was tested by applying excess quantity (150 mg) of the drug to 2 ml of different oils, surfactants, and co-surfactants in screw-capped glass vials accompanied by bath sonicator sonication for 30 sec. The mixtures were shaken in a thermostatically operated water bath at 30 °C for 48 h, followed by 24 hours of equilibrium. The sample mixtures were then centrifuged for 10 min at 3000 rpm and filtered the supernatant liquid through a millipore membrane filter (0.45 microns). Samples were suitably diluted with methanol followed by sonication for 10 min and finally diluted with the same solvent. The final drug concentration was quantified by a UV-visible spectrophotometer at λmax 234 nm **[5-7]**.

Preparation of SEDDS formulations

The different formulations of SEDDS were prepared according to the composition shown in **Table 1**. All the batches were prepared using 10 mg of Lumefantrine. Self-Nano Emulsifying device was prepa-

red by dissolving Lumefantrine at room temperature in the mixture of oil, surfactant, and co-surfactant by stirring using cyclomixer until a clear solution was obtained. The size reduction was supported by probe sonication using a sonic probe sonicator for 1 min till a simple solution was obtained **[8-10]**.

Table 1: Composition of oil, surfactant and co surfactant in the formulation

Batch no.	Drug (mg)	Oil (%)	Surfactant (%)	Cosurfactant (%)
F1	10	70	10	20
F2	10	70	20	10
F3	10	60	20	20
F4	10	60	30	10
F5	10	60	40	-
F6	10	50	30	20
F7	10	50	40	10
F8	10	40	40	20
F9	10	40	50	10

CHARACTERIZATION OF SEDDS OF LUMEFANTRINE

Dispersibility test:

The efficiency of self-emulsification of oral SEDDS was assessed using a USP dissolution apparatus 2. One milliliter of each formulation was added to 500 ml of water at 37±0.5 ˚C. A standard stainless-steel dissolution paddle rotating at 50 rpm to provided gentle agitation to formulation. The formulations in-vitro performance has been measured visually using the following grading system:

Grade A: Rapidly forming (within 1 min) emulsion, having a clear or yellowish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a; yellowish appearance.

Grade C: Fine yellowish milky microemulsion that formed within 2 min **[11]**.

Refractive index

The clarity of prepared batches could be used to access the refractive index. The SEDDS formulations had been mixed with water 100 times. The refractive index of the system was measured by an Abbes Refractometer (1310 E-20 Atago, Japan) by placing 1 drop of solution on the slide and it compare with water **[9]**.

Viscosity and pH:

The viscosities were measured to determine the rheological properties of formulations. Brookfield LVDV 111+ CP viscometer using spindle C 16-1 at 25 °C. The pH of the formulations was measured using pH meter

% Transmittance

The percentage transmittance of prepared SEDDS was determined at 234 nm using UV spectrophotometer (UV- 1601, Shimadzu Corporation, Japan) keeping distilled water as blank **[10]**.

Droplet size, Zeta potential and polydispersity index (PDI).

The droplet size and Zeta Potential was determined through dynamic light scattering (Zetasizer Nano-ZS, Malvern Instruments, Worcestershire, UK) at a scattering angle of 90° at 25℃.All emulsions of SNEDDS were diluted five times in a disposable cuvette with deionized water, and the material was gently mixed. The average droplet size and polydispersity index (PDI) were calculated. Three consecutive measurements for each sample were made, and the results were presented as the mean and standard deviation.

Drug content

The drug content of prepared formulations was found out by accurately weighing sample and dissolving it in 10 ml of methanol. Further, the solution was filtered using Whatman filter paper, and the amount was estimated at 234 nm by the UV spectrophotometer (UV-1601 Shimadzu Corporation, Japan) **[11]**.

Morphological characterization

The morphology of the optimal Lumefantrine-loaded SNEDDS was assessed by TEM (Philips CM12 microscope operating at 120 kV) **[12]**.

In vitro dissolution studies

In vitro dissolution study of all the prepared formulations consisting of Lumefantrine was performed using the Type II dissolution apparatus (Veego Scientific USP Standard DA-60). The prepared formulations were filled in soft gelatine capsules and placed in a dissolution vessel containing 900 ml of phosphate buffer pH 6.8 maintained at 37 ± 0.5°C, further the paddle speed was set at 50 RPM. After the time interval of 5, 10, 20, 30, 40, 50, 60, 70 and 80 min, the samples (5 ml) were withdrawn, and the fresh medium was added to replace the withdrawn sample. Furthermore, the samples were diluted suitably, and the amount of Lumefantrine was determined using a spectrophotometric method at 234 nm (UV-1601 Shimadzu Corporation, Japan).

Similarly, drug release study was performed for active ingredient for comparison with the prepared formulation **[11-12]**.

Stability study

Lumefantrine SNEDDS samples were filled in glass vials with a rubber stopper and then placed in Stability chambers at 25 ±0.5˚C / 60 ± 5 % RH and 40±0.5˚C / 75 ± 5 % RH for 3 months. Duplicate samples were withdrawn at 0, 30, 60, and 90 days to evaluate their physical and chemical stabilities. The physical stability was evaluated by visual inspection for physical changes (such as phase separation and drug precipitation), and a particle size analyzer was used to determine the mean particle

size and zeta potential after dilution with water **[13]**.

RESULTSAND DISCUSSION

Solubility determination of Lumefa-ntrine

The core part of SEDDS is composed of oil in which drug is solubilized hence it is very much important to choose a oil having high solubility for the drug**.** Lumefantrine shows high solubility in Peceol. Tween 80 was selected as the surfactant in trials with different co-surfactants to assess the ability of the co-surfactants to improve the clarity of the system. However, Tween 80 does not show good emulsification as the final system remained hazy. Even though Lumefantrine exhibited highest solubility in Tween 80, it was rejected because its poor emulsification property for Lumefantrine-Peceol. Finally, Labrasol was appointed as surfactant for formulation. Solubility of Lumefantrine was found to be higher in benzyl alcohol compare to other solvents but was rejected in formulation due to its lower acceptability limit and volatile nature. Ethanol was not considered as a co-solvent in the final formulation due to its tendency to diffuse out of the shell and it threatens the integrity of the capsule. Finally PEG-400, was good candidate for a co-surfactant **(Table 2, Figure 1)**.

Drug and surfactant compatibility study:

FTIR was used to test compatibility between the drug excipients. FTIR spectra of SEDDS showed no substantial improvement in major peaks compared to pure drug FT-IR which showed no interaction between drug and excipients. Overall, there was no chemical interference of functional groups between and there was no change in functional properties of drugs **(Figure 2)**.

Dispersibility

The efficiency of self-emulsification of oral SEDDS was assessed by the dispersibility test. Dispersibility of SEDDS of majority of formulation (F2, F4, F5, F7) was Rapidly formed (within 1 min) emulsion, having a clear or yellowish appearance, whereas F3, F6 formed rapidly, slightly less clear emulsion, having a; yellowish appearance. Rest were Fine milky microemulsion that formed within 2 min

Refractive index

Refractive index of some formulations have similar values as that of distilled water (1.3330 ± 0.0002 n.d.) at 28 ± 0.5°C. Whereas the formulations F1, F2, F3, F6, F8, F9 showed some divergence when compared to that of standard and remaining formulations were found to be clear.

Viscosity

The viscosity of the SNEDDS formulations is relevant for the manufacturing of formulation filled in soft or hard gelatin capsules. The results show viscosity range from 183-285 centipoise, depending on the formulation composition. The measured

values are in agreement with the values required for the above-described filling process.

pH

Stability of SEDDS formulations could be greatly affected by pH. All the prepared formulations showed similar pH values in the range of 6.40-6.77 as shown in **Table 3**. Thusthe stability of the formulation was not affected by pH. It can be assumed that the drug is not diffusing in the external phase and remains in the oil phase.

% Transmittance

The clarity of microemulsion was observed by transparency, which can be measured in the form of % transmittance (% T).In the present study, formulation F5 showed the highest transmittance compared to other formulations as shown in **Table 3**.

Particle size, zeta potential and polydispersity index (PDI)

The rate and extent of drug release and absorption was dependent on the globule size which is a critical parameter in the self-emulsification process. It has also been reported that the smaller particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. It can be observed from the results shown in **Table 4** that the smallest particle size (33.84±1.7 nm) with PDI (0.49±0.02) and zeta potential (−22.20 mV) was observed in Formulation F5 as compared to other batches.

Drug content

In the present investigation, the prepared formulations were within the specified limit (90-110%) of drug content according to IP 2018. Formulation F5 contain highest drug 98.86. Drug content of all the SEDDS formulations is shown in **Table 4, Figure 3, 4**.

***In vitro* dissolution rate studies**

Cumulative % drug release of batches F4, F5, F7 was found to be in the range of 93%–99% while that of plain Lumefantrine was found to be 42%. These results were in agreement with the previous findings explaining that the SEDDS formulation, which leads to the spontaneous formation of a nanoemulsion having a smaller droplet size and it leads to a faster release of drug into the aqueous environment as compared with that of pure drug. In the present study, the highest release rate (99.12%) was observed in batch F5 compared to other batches as shown in **Table 5, Figure 5**.

Morphological characterization

The morphology of F5 Lumefantrine loaded self-emulsion was observed by TEM. As shown in **Figure 6**, droplets are spherical with a diameter range of 20–40 nm, according to the light scattering data.

Stability studies

The optimized formulations F5 for Lumefantrine shows no phase separation as well as no drug precipitation and was found to be stable for 3 months and there was no significant change in the particle size and zeta potential as given in **Table 6**.

Table 2: Solubility study of Lumefantrine in various vehicles

Sl. No.	Vehicles	Solubility (mg/ml)
1	Coconut oil	110.34±0.27
2	Olive oil	12.67±0.37
3	Corn oil	18.24±0.61
4	Isopropyl myristate	42.85±1.19
5	Peceol	149.29±1.30
6	Capryol PGMC	23.32±0.26
7	Labrafil M 2125	25.19±0.56
8	Labrasol	63.32±0.41
9	Tween 80	94.21±1.69
10	Propylene glycol	0.831±0.19
11	Ethanol	3.841±0.29
12	PEG 400	3.839±0.18
13	Glycerol	2.845±0.12
14	Benzyl alcohol	79.24±1.41

*Mean±SD, n=3

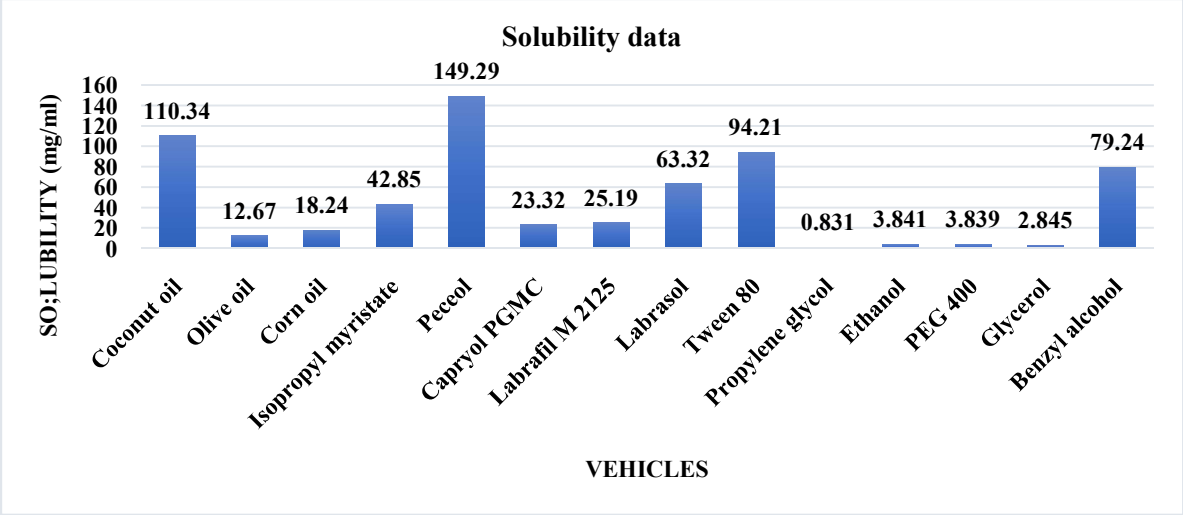

Figure 1: Solubility studies of Lumefantrine in various vehicles

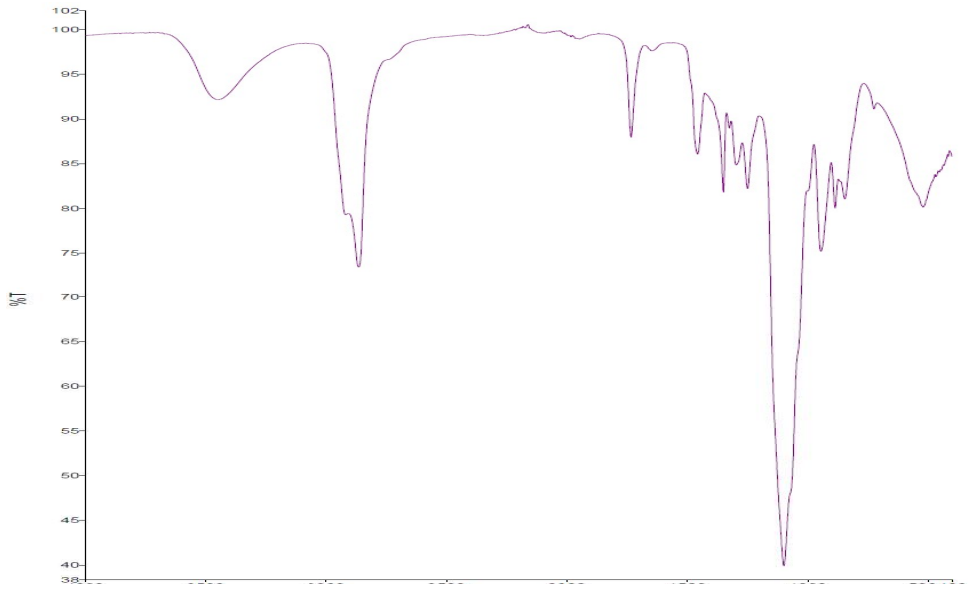

Figure 2: Infrared spectrum of Lumefantrine + oil + s-mix

Table 3: Dispersibility, Refractive index, Viscosity, Ph and % Transmittance of Lumefantrine-SEDDS formulations

Batch no.	Dispersibility	Refractive index	pH	Viscosity	% Transmittance
F1	C	1.3341±0.005	6.57±0.08	252.3±2.56	87.13±0.13
F2	A	1.3363±0.003	6.69±0.01	212.3±1.52	97.76±0.21
F3	B	1.3352±0.004	6.51±0.12	238.6±2.36	92.16±0.03
F4	A	1.3335±0.001	6.54±0.26	198.5±1.64	97.56±0.25
F5	A	1.3332±0.002	6.43±0.06	186.6±1.52	98.65±0.25
F6	B	1.3356±0.004	6.53±0.25	223.5±1.23	96.13±0.16
F7	A	1.3336±0.001	6.66±0.54	183.9±2.65	97.18±0.76
F8	C	1.3366±0.003	6.70±0.84	233.2±1.02	92.00±0.36
F9	C	1.3364±0.002	6.77±0.03	285.7±1.32	84.12±.031

The mean of 3 values, n=3±SD

Table: 4 Particle size, Zeta potential, PDI, Drug content of Lumefantrine-SEDDS formulations

Batch no.	Particle size (nm)	Zeta potential (mV)	PDI	Drug content
F1	132.03±1.6	-26.61	0.58±0.08	98.00±0.89
F2	89.86±1.9	-10.28	0.33±0.04	96.90±0.66
F3	87.19±0.2	-18.35	0.54±0.01	97.13±0.65
F4	57.39±1.5	-21.6	0.31±0.05	97.21±0.65
F5	33.84±1.7	-22.2	0.49±0.02	98.86±0.58
F6	70.08±0.5	-19.26	0.62±0.01	97.53±0.70
F7	53.21±1.5	-24.3	0.29±0.05	98.13±0.56
F8	97.48±21	-14.38	0.47±0.08	96.10±0.75
F9	98.36±56	-10.29	0.49±0.02	97.16±0.40

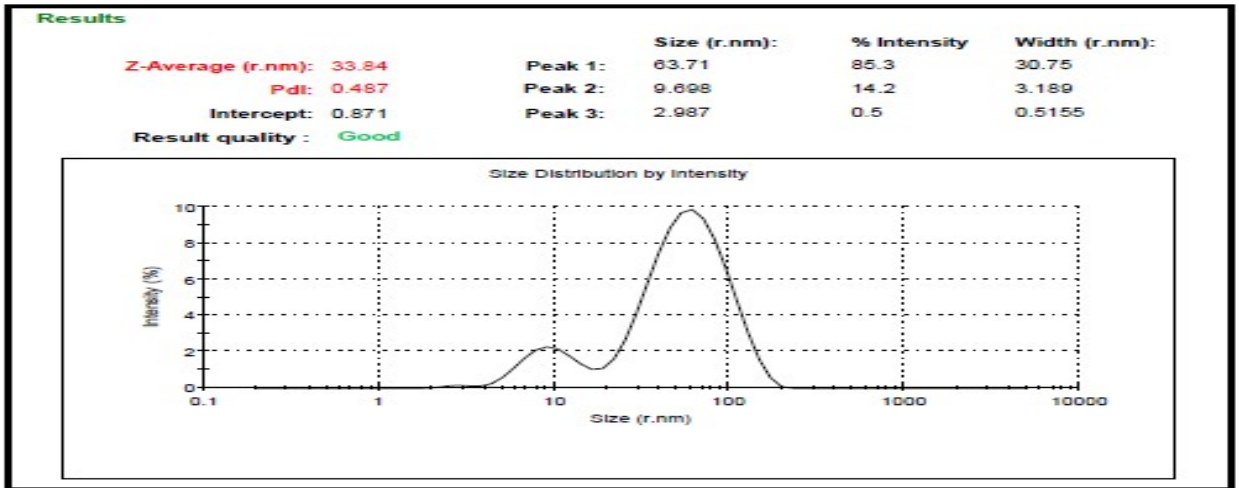

Figure 3: Particle size of F5 formulation

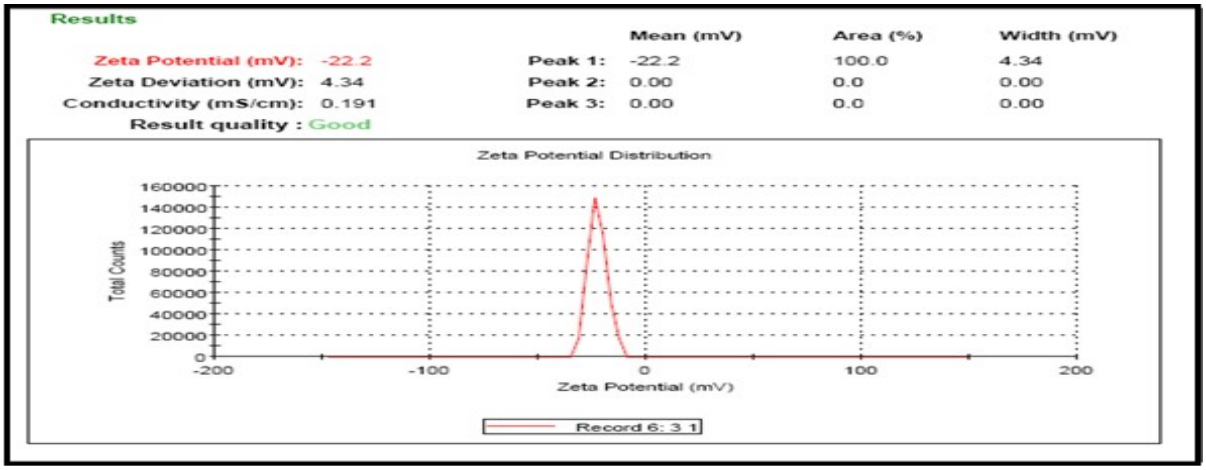

Figure 4: Zeta potential of F5 formulation

Table 5: Cumulative percent release of Lumefantrine loaded SNEDDS from various formulations and pure drug.

Time (min)	F4	F5	F7	Pure drug
0	0	0	0	0
5	22.89±0.54	23.21±0.23	21.21±0.21	5.69±0.23
10	32.56±0.21	38.36±0.52	32.36±0.56	8.56±0.56
20	48.65±1.23	47.31±0.12	49.31±0.32	12.33±0.45
30	65.23±0.65	56.66±0.24	67.66±0.89	18.23±0.69
40	77.89±0.58	65.79±1.02	74.66±0.41	23.36±0.75
50	79.98±0.65	79.50±1031	79.66±0.36	27.46±0.54
60	88.26±0.12	85.72±0.69	83.63±0.56	32.42±0.69
70	85.99±1.68	92.03±0.54	88.54±0.14	38.12±0.45
80	93.45±1.12	99.12±0.12	96.26±0.89	41.62±1.23

The mean of 3 values, n=3±SD

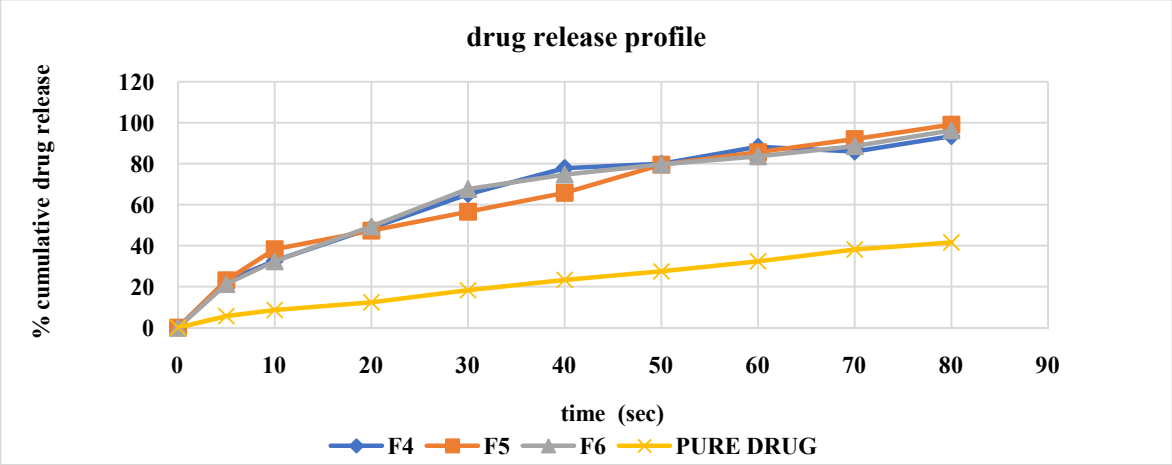

Figure 5: Cumulative percent release of Lumefantrine loaded SNEDDS from various formulations and pure drug

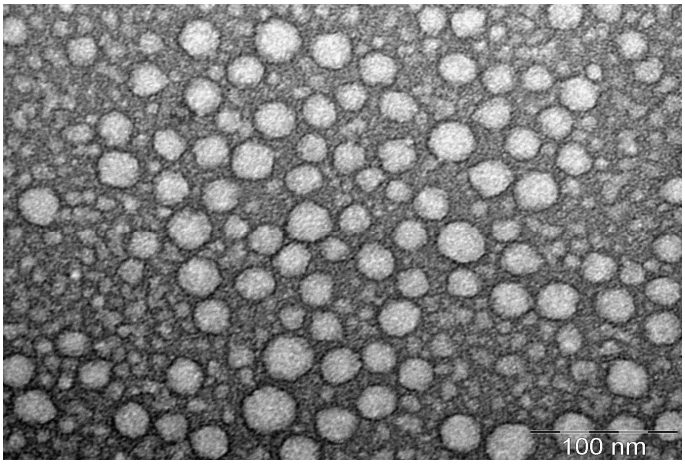

Figure 6: TEM image of F5 Lumefantrine-SNEDDS

Table 6: Effects of storage conditions on the dynamic characteristics of nanoemulsion obtained from F5

Storing Time [months]	Temp=4°C		Temp=25°C		Temp =40 °C	
	Droplet size (nm)	Zeta potential (mV)	Droplet size (nm)	Zeta potential (mV)	Droplet size (nm)	Zeta potential (mV)
Initially	33.84±1.7	-22.2	33.84±1.7	-22.2	33.84±1.7	-22.2
1	33.98±1.7	-22.2	33.91±1.7	-22.2	34.98±1.37	-23.2
2	34.23±0.34	-22.6	34.10±1.7	-22.3	35.83±1.34	-24.6
3	36.64±1.86	-23.2	35.36±1.7	-22.9	39.54±1.26	-25.8

CONCLUSION

Lumefantrine is an orally administered flourene derivative anti-malarial drug for the treatment of falciparum malaria, but its solubility and oral bioavailability are poor. The objective of our investigation was to formulate a self-emulsifying drug delivery system (SEDDS) of Lumefantrine using minimum surfactant concentration that could improve its solubility, stability and oral bioavailability. The composition of optimized formulation (F5) consist of Peceol as oil, Labrasol as surfactant, containing 10 mg of Lumefantrine showing drug release for liquid SEDDS formulation (99.13%), droplet size (33.84 nm), Zeta potential (-22.2 mV), viscosity (156.2 cP) and infinite dilution capability. *In-vitro* drug release of the F5 was highly significant as compared to pure drug. Stability studies were performed for optimized formulation.The present SNEDDS would be a promising novel system to improve the lipophilic drug's dissolution rate and potentially the bioavailability.

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