

# Enhancing Solubility and Bioavailability of Artemether and Lumefantrine through a Self-nano Emulsifying Drug Delivery System

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## Gaikwad *et al.*: Self-nano Emulsifying Drug Delivery System of Artemether and Lumefantrine

In the present study artemether and lumefantrine self-nano emulsifying drug delivery system formulations were prepared using combination of these drugs with Capmul medical countermeasure, oleic acid and Tween 80. The particle size and zeta potential of these formulations was found to be 15.2 nm and  $-22.8$  mV. The solubility and *in vitro* dissolution performance of both drugs in self-nano emulsifying drug delivery system formulations was improved significantly as compared to pure drugs and marketed product and the *in vivo* studies confirmed it. *In vivo* studies in rats revealed that there was an increase in bioavailability of self-nano emulsifying drug delivery system formulations compared to pure drugs with the area under the curve of artemether from formulation was  $598.89 \pm 114.33$  in comparison to that of pure artemether  $190.82 \pm 36.57$  and the area under the curve for lumefantrine from the formulations was  $190.82 \pm 36.57$  in comparison to that of the pure lumefantrine  $68.71 \pm 18.63$ . The  $C_{max}$  was enhanced for artemether from  $13.11 \pm 2.22$  to  $110.31 \pm 40.88$  and for lumefantrine from  $2.39 \pm 1.61$  to  $18.22 \pm 2.32$ .

**Key words:** Artemether, lumefantrine, malaria, nanotechnology, solubility, *in-vivo* bioavailability

Approximately 40-70% of new therapeutic molecules studied in recent years belong to class II or Class IV of Biopharmaceutical Classification System (BCS), exhibiting low solubility that restricts absorption from gastrointestinal (GI) system after oral administration<sup>[1,2]</sup>. There are many possible factors for poor or erratic bioavailability. In order to achieve high bioavailability and low variability for oral pharmaceutical products, API must be dissolvable and stable in GI lumen to get absorbed adequately. The bioavailability of these candidates can be enhanced by lipid based drug delivery system along with nanotechnology, which provides additive effect on bioavailability<sup>[3,4]</sup>. Several techniques have been used to improve the bioavailability of poorly soluble therapeutic compound such as particle size reduction, liposomes, nano-micelles and self-emulsifying drug delivery system<sup>[5-8]</sup>.

One of the promising approaches amongst these are self-nano emulsifying drug delivery system (SNEDDS), a homogeneous mixtures of oils, drugs, surfactants and co surfactants, which are anhydrous in nature and have emerged as a promising approach in nano emulsions for

oral drug delivery. Oil-in-Water (O/W) nano emulsions will be spontaneously formed when SNEDDS is exposed to GI fluids. The physicochemical properties of drugs encapsulated in nano emulsions significantly change and overcome the multiple bio-barriers in GI tract leading to improved oral bioavailability<sup>[9-12]</sup>.

Malaria is a life-threatening disease caused by *Plasmodium* parasites that are, transmitted to people through the bites of infected *Anopheles* mosquitoes. The massive antimalarial market is largely made up of poor people, making it less pleasing to pharmaceutical companies and consequently their investment in antimalarial research is declining<sup>[13]</sup> and also increasing resistance to existing drugs coupled with the scarcity of new drugs/drug combinations, the onus of malaria control lies largely on wise use of available

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antimalarials through the design of nanotechnology based drug delivery systems and combination therapy. Antimalarial combination therapy, which has been widely explored involves simultaneous use of two or more blood schizontocidal drugs with independent modes of action against distinct biochemical targets in the malarial parasite. Among the developed combinations, WHO has banned monotherapy and recommend few rational combinations and artemether lumefantrine combination is one of them. The rationale for combining these two antimalarials with different modes of action was to couple the synergistic fast onset of action of artemether with the long duration of action of lumefantrine. Artemether is essential for rapid clearance of parasitaemia and rapid resolution of symptoms. Artemether is effective against drug resistant malaria and additionally it reduces gametocyte carriage. However the drug exhibits a short half-life of 2-3 h. It was therefore combined with lumefantrine, which acts slowly and has a longer half-life. The long-acting effect of lumefantrine may prevent recrudescence and development of resistance<sup>[14,15]</sup>.

Artemether, a BCS Class II drug exhibits low aqueous solubility with higher permeability and quickly metabolized in GIT, while lumefantrine has low solubility and low permeability (BCS Class IV). Thus, it was planned to design an oral formulation which enhances the solubility of both the drugs and also overcomes the metabolism of artemether in the GIT with enhanced permeability of lumefantrine. These biopharmaceutical challenges are removed by versatile formulation approaches to retain the physicochemical properties of the drugs while simultaneously overcoming the biopharmaceutical challenges. Thus, the present work is focused on development of lipid-based drug delivery systems of artemether and lumefantrine in combination to increase the solubility, facilitate absorption of both these drugs and to overcome the drawback of inconsistent bioavailability<sup>[16-19]</sup>.

## MATERIALS AND METHODS

Artemether was procured as a gift sample from Ipca Laboratories Ltd., Mumbai, India. Lumefantrine and magnesium aluminum silicate (*CAS No*: 1327-43-1) were procured as gift samples from Zim Laboratories, Nagpur, India. Tween 80 (*CAS No*-9005-65-6) and Oleic acid (*CAS No*: 112-80-1) was purchased from Merck India Ltd, Mumbai, India. Capmul MCM (*CAS No*: 26402-22-2) was obtained from Abitec Corporation, USA. All the other chemicals used in this study were of AR grade.

## Determination of saturation solubility of artemether and lumefantrine in different systems:

The solubility of artemether and lumefantrine in various oils, surfactants, co-surfactants and co-solvents was determined by dissolving an excess amount of each drug in 2 ml of each selected solvent systems in 5-ml stoppered vials separately (Table 1). The contents of the vials were mixed on a vortex mixer and further stirred on an orbital shaker at  $37\pm 1^\circ$  for 72 h to reach equilibrium. The samples were then centrifuged at 3000 rpm for 15 min, supernatants were filtered through a membrane. The concentration of artemether and lumefantrine in different solvent systems was determined using a HPLC (Shimadzu LC2100 at 214 nm, reversed phase C18, 4.6×250 mm, 10 µm particle size) at 25°, employing a mobile phase containing acetonitrile:double distilled water:glacial acetic acid (75:25:0.2) at a flow rate of 1 ml/min. The retention time for artemether and lumefantrine were found to be 9.0 and 11.2 min, respectively<sup>[15]</sup>.

## Construction of ternary phase diagram for identification of micro emulsions zone:

On the basis of solubility studies, components of emulsions such as oils, surfactants and co surfactants with greater solubility for artemether and lumefantrine were selected. The blends of surfactants and co surfactants ( $S_{mix}$ ) were prepared then mixed with the oily phase by adding small amounts with constant stirring. The varied proportions of oil: $S_{mix}$  were titrated with distilled water with stirring to produce clear and transparent

**TABLE 1: SOLUBILITY OF ARTEMETHER AND LUMEFANTRINE IN DIFFERENT OILS AND SURFACTANTS**

Oils/surfactants/ co-solvents	Solubility of artemether (mg/ml)	Solubility of lumefantrine (mg/ml)
Castor oil	32.3±0.52	10.31± 0.86
Arachis oil	41.23±0.32	32.85± 0.21
Corn oil	11.34±0.12	23.91± 0.87
Oleic acid	17.90±0.67	597.85±0.34
Captex 300	35.45±0.23	12.31±56
Capmul MCM	315.34±0.07	16.39±0.48
Gelucire	32.45±0.32	19.32±0.21
Isopropyl myristate	18.54±0.87	50.11±0.32
Acconon MC8	8.22±0.43	15.22±0.67
Tween 80	233.08±0.98	110.87±43
Tween 20	4.67±0.13	10.18±0.13
Span 80	9.88±0.90	5.67±0.38
Cremophore EL	232.40±0.29	45.52 ±0.29
Cremophore RH 40	21.45±0.21	53.32±0.34

Mean±SD, n=3

solutions. From these observations, the ternary phase diagram was constructed<sup>[20]</sup>.

### **Formulation of liquid SNEDDS of artemether and lumefantrine:**

Liquid SNEDDS were prepared by dispersing the required quantity of artemether and lumefantrine in 20 % w/w Capmul MCM (co-surfactant). The mixture was homogenized and oil:surfactant blend (oleic Acid 20 % w/w:Tween 80 60 % w/w) was added in small portions with constant stirring. The blends were mixed thoroughly on a magnetic stirrer to obtain resultant emulsion<sup>[21]</sup>.

### **Characterization of liquid SNEDDS:**

The droplet size distributions and Zeta potential of the resultant emulsions were determined using a particle size analyzer (Nanosizer SZ-100)<sup>[22]</sup>. The percent drug content of artemether and lumefantrine in SNEDDS was estimated by the dissolving SNEDDS equivalent to 120 mg of artemether and 20 mg lumefantrine in the mobile phase and analyzing the drug content using HPLC.

### **Preparation and characterization of solid SNEDDS:**

The liquid SNEDDS was adsorbed on the carrier by physical mixing to form solid SNEDDS (S-SNEEDS) using the adsorption method with Neusilin US2 as a carrier mixed in the ratio of 1:1. A free flowing powder of S-SNEEDS was obtained<sup>[20,23]</sup>. The physical properties of S-SNEEDS such as angle of repose, bulk and tapped density were determined using reported methods. Hausner's ratio, and Carr's index was determined to understand the flow properties of S-SNEEDS<sup>[23]</sup>.

Particle size and the zeta potential of the prepared S-SNEEDS were determined by diluting with 100 ml distilled water and sonicating to form droplets. The droplet size distributions and zeta potential of the resultant emulsion was determined on a particle size analyzer. Percent drug content of artemether and lumefantrine in S-SNEEDS was determined using HPLC.

### ***In vitro* drug release:**

*In vitro* dissolution studies were performed using the USP XXII type II apparatus at 50 rpm, 37±0.5° in order to ensure quick release of the drug in to the dissolution medium (900 ml of pH 7.2 phosphate buffer containing 1 % w/v sodium lauryl sulphate] for S-SNEEDS, pure artemether and lumefantrine and the marketed

formulation Lumither®. Aliquots were withdrawn at predetermined intervals and analyzed using HPLC to determine cumulative percent drug release<sup>[24]</sup>.

### **Differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR):**

The drugs and formulation were exposed in standard aluminum pan and scanned at a speed of 10°/min and heat flow from 0 to 200° on a DSC (Netzsch STA 409) and crystal transformation and thermal behavior was studied. FTIR (Bruker Vertex 70) spectra of artemether, lumefantrine and formulation were run by preparing a pellet of potassium bromide and analysed over a range 4000-400 cm<sup>-1</sup>. The spectra were recorded and the functional groups were determined.

### **Scanning electron microscopy (SEM) and X-ray diffractometry (XRD):**

The surface morphology of artemether, lumefantrine and formulation was studied using SEM (Phenom G2 pure) by sprinkling S-SNEEDS powder on a double adhesive plate stuck on an aluminum stub, further coated with platinum 10°A thick under high vacuum. XRD was used for determining structure of crystals based on pattern of diffraction and was carried on a X-ray Diffractometer (Rigaku Mini Flex 600). X-ray scattering measurements of artemether, lumefantrine and formulation were carried out at a voltage of 40 kV and current of 25 mA using Cr as a tube anode material. Artemether, lumefantrine and formulations were exposed at angles of 10-70° to Cu -K $\alpha$  radiation<sup>[25]</sup>.

### **Bioavailability studies:**

Animal experiments were performed as per the guidelines of the Institutional Animal Ethical Committee, Zydus Research Centre Zydus Cadila, Ahmedabad, India (AEC Approval no: ZRC/TOX/NP/093/12-2K13). Male Sprague Dawley rats (170-200 g) were kept in air-conditioned animal quarters at a temperature of 22±2° and a relative humidity of 50±10 % under fasting conditions were used. The rats were allowed to acclimatize for 7 d and then fasted but with free access to water for 8 h prior to the experiment. All rats were divided in to groups of 5 animals and administered orally doses of 3.6 mg/kg of artemether (group 1), 21.6 mg/kg of lumefantrine (group 2) marketed formulation of artemether and lumefantrine (Lumither®, group 3) and the optimized formulation of S-SNEEDS containing artemether and lumefantrine (group 4). All formulations were dispersed in pure water containing 0.5 % sodium carboxymethyl cellulose,

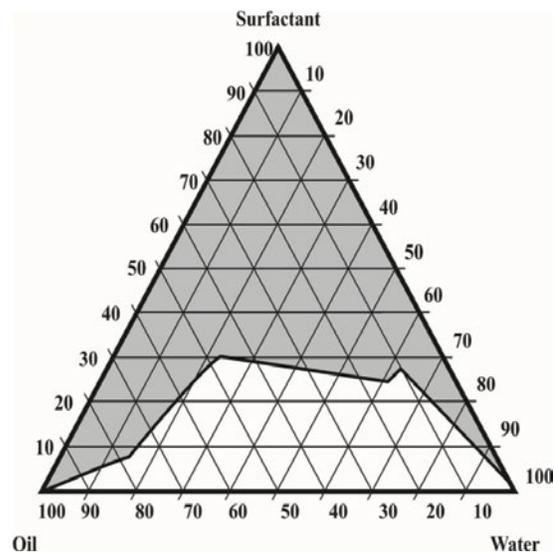
and immediately administered by oral gavage. Rats were anesthetized and blood samples were collected at desired time intervals from the tip of the tail into heparinized glass capillary tubes and centrifuged. Protein from plasma aliquot was removed by acetonitrile precipitation. The supernatant was filtered and injected into HPLC for analysis of artemether and lumefantrine in plasma. Mobile phase used was a binary gradient of methanol and 0.025M ammonium acetate, pH-3.8, flow rate 1 ml/min, monitored at 216 nm in a UV detector. For the analysis of data kinetics software was used<sup>[26]</sup>.

The formulation was filled in capsules (size 00) and stability studies were carried out according to ICH guidelines at accelerated conditions of  $40 \pm 2^\circ$  and  $75 \pm 5$  % RH in a stability chamber and at the end of 1, 3, 6 months drug content was determined .

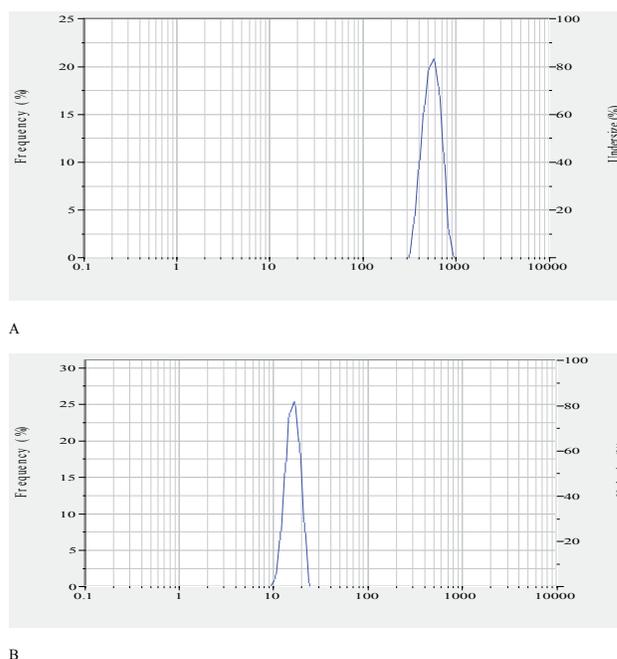
## RESULTS AND DISCUSSION

Different oils, surfactants and co surfactants were used to find out the solubility of artemether and lumefantrine. Among the oil phases studied, saturation solubility of artemether was found to be superior in Capmul MCM and for lumefantrine, oleic acid showed maximum solubility. The saturation solubility of artemether and lumefantrine was found to be higher in Tween 80 out of the surfactants tested (Table 1). For the development of liquid SNEDDS, the compositions of micro emulsion zones from phase diagram (fig. 1) were selected, which were, Tween 80, oleic acid and Capmul MCM. The droplet size of SNEDDS (15.6 nm) indicated the formation of SNEDDS precisely as shown in fig. 2. The observed value of zeta potential was found to be -17.3 mV. The drug content of the SNEDDS formulations suggested uniform distribution of artemether and lumefantrine. Artemether content of the formulation was found to be  $98.32 \pm 0.76$  % and that of lumefantrine was found to be  $98.56 \pm 0.36$  %.

The S-SNEDDS formulation F1 indicated good flow properties and complied with powder characteristics such as bulk density of  $0.402 \pm 0.0024$  cm<sup>3</sup>, tapped density of  $0.459 \pm 0.0030$  cm<sup>3</sup> with Carr's index  $12.41 \pm 0.813$ , Hausner's ratio  $1.14 \pm 0.010$  and angle of repose of  $28$ <sup>[23]</sup>. The size of F1 formulation was found to be 15.2 nm as shown in fig. 2. Particle size of S-SNEDDS seemed to be less affected by solidification of liquid SNEDDS providing additive effect on bioavailability and zeta potential was found to be -22.8 mV. The artemether and lumefantrine contents of S-SNEDDS were virtually identical with those obtained for liquid SNEDDS. In



**Fig. 1: Ternary phase diagram**  
Ternary phase diagram for oleic acid/Tween 80/Capmul MCM water system. Shaded area represents microemulsion region



**Fig. 2: Particle size analysis of SNEDDS and formulation F1**  
Particle size analysis of A. SNEDDS and B. the formulation F1 containing S-SNEDDS

the formulation the content of artemether was found to be  $98.87 \pm 0.34$  % and that of lumefantrine was found to be  $97.08 \pm 0.24$ %.

SNEDDS formulation showed highest cumulative drug release ( $96.34 \pm 0.65$ %) followed by Lumither® ( $72.56 \pm 0.12$ %) and pure artemether ( $24.34 \pm 0.96$ %) in 60 min of the study. Similarly SNEDDS formulation showed highest cumulative drug release ( $95.64 \pm 0.06$ %) followed by Lumither® ( $92.83 \pm 0.09$ %) and pure

lumefantrine ( $15.94 \pm 0.02$ ) in 120 min of the study as shown in Tables 2 and 3. Self emulsification and dissolution in SNEDDS was observed which was enhanced due complexation and prevention of drug precipitation. Thus, from dissolution studies it can be concluded that aqueous solubility and dissolution rate of drugs were significantly enhanced.

The DSC thermogram of artemether showed typical characteristics of a crystalline substance indicated sharp endothermic peak at  $89.7^\circ$  whereas, lumefantrine showed a sharp endothermic peak at  $140.1^\circ$  and onset at  $131.1^\circ$ , which were identical to the reported value. SNEDDS represented no such peak, which indicated that the change in melting behavior of drug and inhibition of crystallization. The disappearance of the melting endotherm in the DSC scan of SNEDDS of artemether and lumefantrine suggested that the crystalline drug was converted to the amorphous state. DSC scans of artemether, lumefantrine and SNEDDS are shown in fig. 3.

Artemether was characterized by crystals of bigger size and regular shape with an apparently smooth

**TABLE 2: CUMULATIVE DRUG RELEASE FROM SNEDDS, LUMITHER® AND PURE ARTEMETHER**

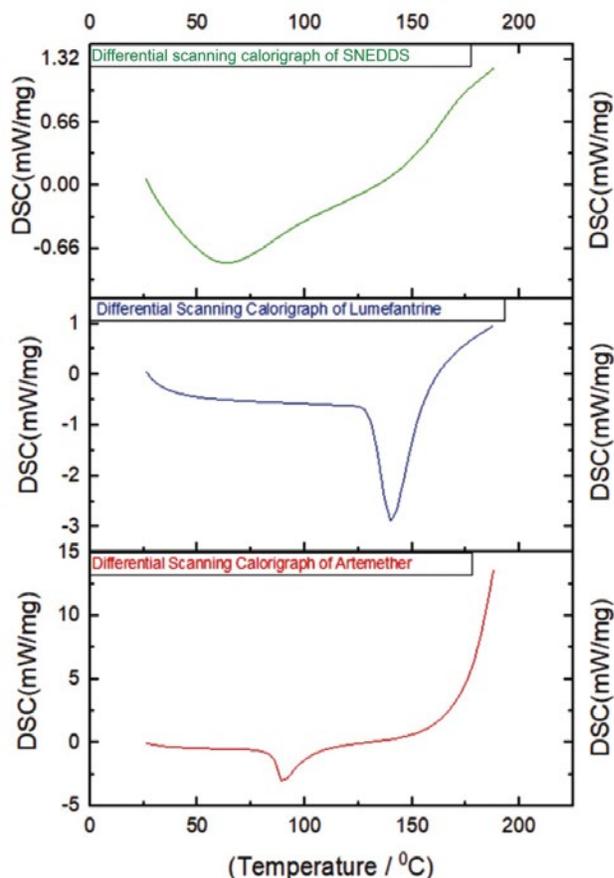
Time (min)	CDR pure artemether (%)	CDR SNEDDS (%)	CDR Lumither® (%)
0	0	0	0
10	$4.56 \pm 0.39$	$64.32 \pm 0.76$	$22.45 \pm 0.08$
20	$5.34 \pm 0.98$	$72.03 \pm 0.01$	$29.34 \pm 0.40$
30	$6.23 \pm 0.77$	$79.21 \pm 0.99$	$40.43 \pm 0.45$
40	$12.35 \pm 0.76$	$88.66 \pm 0.63$	$52.56 \pm 0.87$
50	$19.76 \pm 0.23$	$93.72 \pm 0.29$	$64.74 \pm 0.62$
60	$24.34 \pm 0.96$	$96.34 \pm 0.65$	$72.56 \pm 0.12$

CDR is cumulative drug release, Mean $\pm$ SD, n=3

**TABLE 3: CUMULATIVE DRUG RELEASE OF SNEDDS, LUMITHER® AND PURE LUMEFANTRINE**

Time (min)	CDR pure lumefantrine (%)	CDR SNEDDS (%)	CDR Lumither® (%)
0	0	0	0
10	$2.46 \pm 0.56$	$63.67 \pm 0.24$	$21.87 \pm 0.71$
20	$4.23 \pm 0.76$	$69.67 \pm 0.40$	$27.67 \pm 0.44$
30	$5.56 \pm 0.05$	$73.65 \pm 0.43$	$38.56 \pm 0.54$
40	$5.76 \pm 0.09$	$82.54 \pm 0.45$	$49.56 \pm 0.09$
50	$6.44 \pm 0.21$	$89.65 \pm 0.67$	$62.54 \pm 0.76$
60	$7.94 \pm 0.12$	$92.78 \pm 0.09$	$70.78 \pm 0.83$
70	$8.62 \pm 0.08$	$94.56 \pm 0.70$	$74.45 \pm 0.86$
80	$9.13 \pm 0.72$	$94.18 \pm 0.32$	$78.43 \pm 0.49$
90	$10.94 \pm 0.87$	$94.71 \pm 0.45$	$80.43 \pm 0.05$
100	$11.89 \pm 0.21$	$95.15 \pm 0.91$	$85.44 \pm 0.09$
110	$13.74 \pm 0.98$	$95.39 \pm 0.21$	$88.74 \pm 0.12$
120	$15.94 \pm 0.02$	$95.64 \pm 0.06$	$92.83 \pm 0.09$

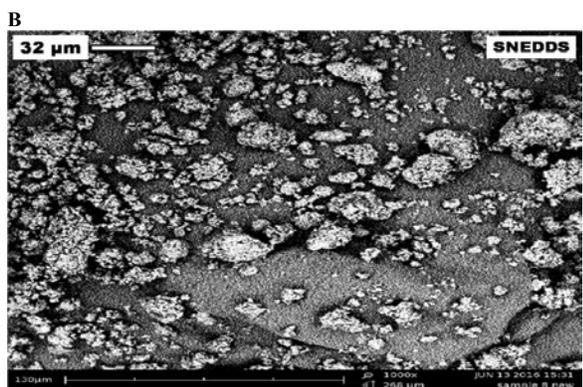
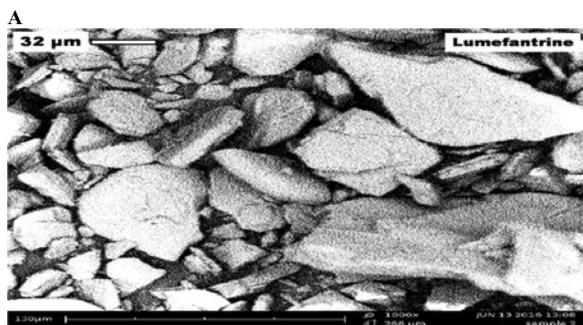
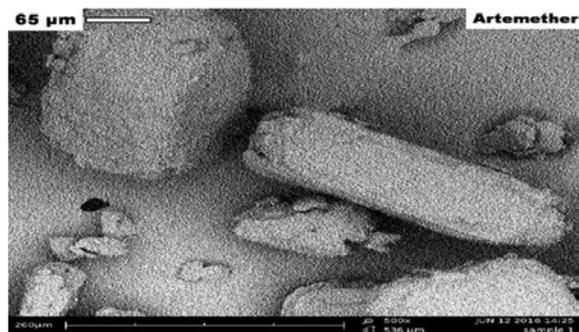
CDR is cumulative drug release, Mean $\pm$ SD, n=3



**Fig. 3: Differential scanning calorimetry of artemether, lumefantrine and SNEDDS**

surface. SEM micrographs of lumefantrine revealed large crystalline blocks characterizing its identity and crystalline character. The photomicrograph of S-SNEDDS indicated uniform surface. Artemether and lumefantrine crystals adhered on the surface of Neusilin US2 suggested that the entire drug was distributed on the adsorbent uniformly over the carrier mass and well-separated particles with no agglomeration. The reduced crystallinity of artemether and lumefantrine in formulation was further confirmed from the results of XRD and DSC studies. SEM photomicrographs of artemether, lumefantrine and S-SNEDDS is shown in fig. 4.

FTIR was carried out to evaluate the drug excipient compatibility. The FTIR spectra of artemether and lumefantrine revealed the presence of major functional groups present in structure supporting their identity (Table 4). FTIR spectrum of S-SNEDDS revealed that there was no considerable change in major peaks when compared to FTIR of pure drugs and excipient, which confirmed that there was no modification or interaction between drugs and excipients (Table 5). Thus, there was no chemical interference of functional



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Fig. 4: SEM pictomicrographs of drugs and SNEDDS  
Scanning electron microscopy pictomicrographs of  
A. artemether, B. lumefantrine and C. SNEDDS of  
artemether and lumefantrine

TABLE 4: INTERPRETATION OF FTIR SPECTRA OF ARTEMETHER AND LUMEFANTRINE

Drugs	Group	Wavenumber (cm <sup>-1</sup> )	Stretching/deformation
Artemether	-CH <sub>2</sub> , -CH <sub>3</sub>	2949.30	Stretching aliphatic
	C-O-C	1157.3	Stretching (ether linkage)
	-CH <sub>2</sub> , -CH <sub>3</sub>	1375.38-1450.77	Bending vibrations
	=C-H	651.22	Bending
Lumefantrine	O-H	3402.70	Aromatic stretching
	C-O	1155.86	Stretching
	C-H	2955.75	Aliphatic stretching
	C-H	3094	Aromatic stretching

TABLE 5: INTERPRETATION OF FTIR SPECTRUM OF ARTEMETHER AND LUMEFANTRINE IN SNEDDS

Drugs	Group	Wavenumber (cm <sup>-1</sup> )	Stretching/deformation
Artemether	-CH <sub>2</sub> , -CH <sub>3</sub>	2927.54	Aliphatic stretching
	C-O-C	1157.3	Ether stretching
	-CH <sub>2</sub> , -CH <sub>3</sub>	1351.43-1464.84	Bending vibrations
	=CH-H	956.98	Alkene bending
Lumefantrine	C-H	3009.570	Aromatic stretching
	C-O	1139.22	Stretching
	C-H	2855.07	Aliphatic stretching
	C=C	1575.43	Aromatic stretching

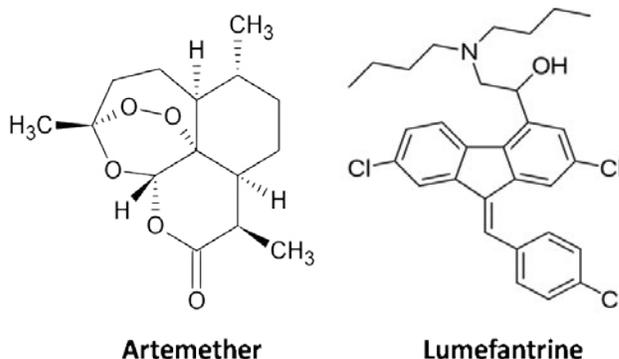


Fig. 5: Structures of artemether and lumefantrine

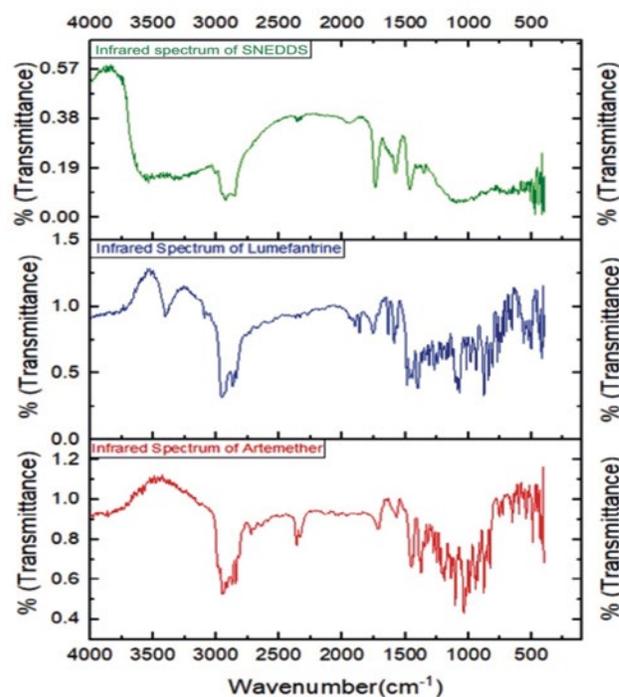
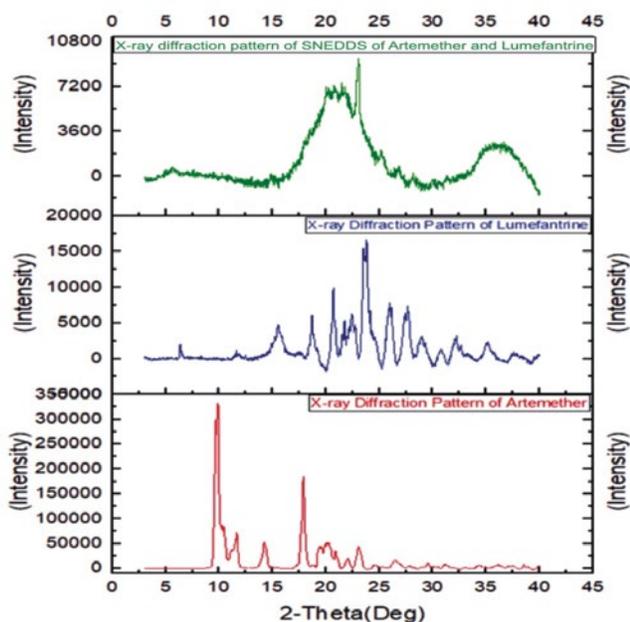


Fig. 6: FTIR spectra of artemether, lumefantrine and SNEDDS

groups and properties of drugs, respectively. Structure of artemether and lumefantrine is shown in fig. 5 and the FTIR Spectra of artemether, lumefantrine and S-SNEDDS are shown in fig. 6.

The X-ray diffractogram of artemether verified the physical nature of artemether; which represented numerous intense and sharp multiple peaks corresponding to the crystalline nature of the drug. The XRD patterns of artemether showed very strong characteristic diffraction peaks at  $2\theta$  of  $9.88^\circ$ ,  $17.64^\circ$ ,  $18.04^\circ$  and  $19.68^\circ$ . It signified that artemether is purely a crystalline compound. The XRD of lumefantrine indicated specific peaks of crystallinity at  $2\theta$  of  $6.9^\circ$ ,  $8.5^\circ$ ,  $10.5^\circ$ ,  $12.91^\circ$ ,  $13.64^\circ$ ,  $18.12^\circ$ ,  $19.21^\circ$ ,  $20.72^\circ$ ,  $21.6^\circ$  and  $32.14^\circ$  also indicating its crystalline nature.

X-ray diffraction pattern of S-SNEDDS of artemether and lumefantrine verified the physical state of these drug in S-SNEDDS. Pure drugs gave sharp peaks, which indicated highly crystalline nature, whereas formulation did not showed significant crystalline peaks of these drugs and prepared SNEDDS exhibited a reduction in both number and intensity of peaks. The conversion of crystalline drugs in to amorphous state was confirmed due to diffused pattern observed in X-ray crystallography of SNEDDS. Hence, it was confirmed that the molecularly dispersed state of artemether and lumefantrine in the formulation and its effective solubilization. X-ray crystallographs of artemether, lumefantrine and S-SNEDDS is shown in fig. 7.

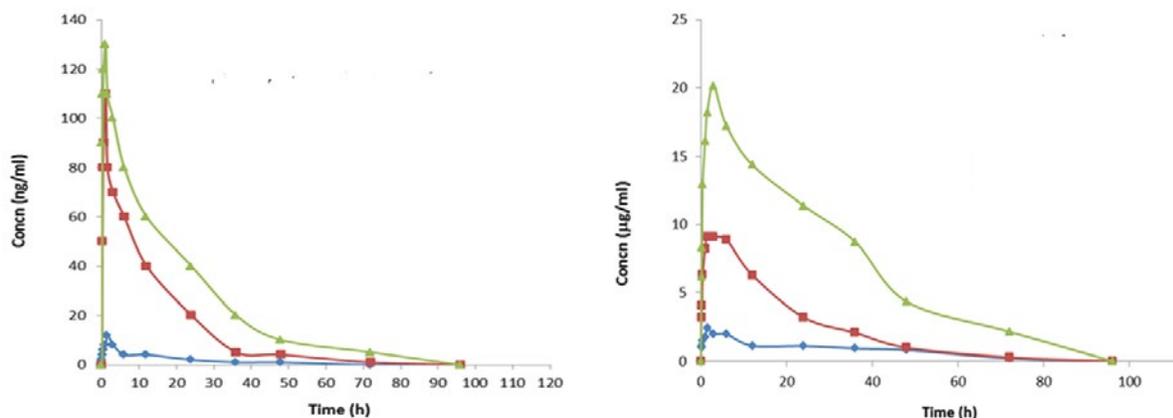


**Fig. 7: X-ray diffraction patterns of artemether, lumefantrine and SNEDDS of artemether and lumefantrine**

*In vivo* bioavailability study of artemether and lumefantrine, S-SNEDDS and marketed formulation was performed to obtain the AUC (area under the plasma concentration time curve up to the last quantifiable concentration) and  $C_{max}$  (observed maximum plasma concentration) following oral administration and is depicted in fig. 8. Formulation SNEDDS F1, artemether, lumefantrine and marketed formulation Lumither<sup>®</sup> were used in this study. The  $t_{max}$  values of artemether and lumefantrine were statistically similar across the formulation groups. The  $C_{max}$  and AUC value of drugs following oral administration of SNEDDS were significantly higher than that of the Lumither<sup>®</sup> and artemether and lumefantrine. *In vivo* drug release study of SNEDDS, Lumither<sup>®</sup> and pure drug Artemether and Lumefantrine is shown in Table 6.

It was found that during the first 1 h artemether released from the SNEDDS was the highest as compared to pure artemether and Lumither<sup>®</sup> and it was the highest till 72 h. Thus, it can be concluded that there was ten-fold increase in bioavailability of artemether from SNEDDS formulation as compared to pure artemether and its marketed formulation Lumither<sup>®</sup>. It was observed that during the first 1 h lumefantrine release from the SNEDDS was the highest as compared to pure lumefantrine and Lumither<sup>®</sup> and showed high till 72 h. Thus, there was ten-fold increase in bioavailability of lumefantrine from the SNEDDS formulation as compared to pure lumefantrine. These studies indicated that drug diffused at a faster rate from the SNEDDS as compared to the pure drug and marketed formulation due to smaller particle size of micro emulsion and enhanced solubility of drug and thereby resulted in increased bioavailability.

The solid SNEDDS produced showed beneficial characteristics of self-emulsifying system due to enhanced surface area with formation of nano particles, which enhanced diffusion, surfactants enhanced mucosal permeability and absorptivity in lymphatic fluid<sup>[27]</sup>. Results of stability studies of capsules containing S-SNEDDS at  $40\pm 2^\circ$  and  $75\pm 5\%$  RH indicated stability of formulation. The percent drug content was found to be  $98.78\pm 0.81$ ,  $97.04\pm 0.43$ , and  $97.32\pm 0.21\%$  for artemether and  $98.53\pm 0.33$ ,  $98.32\pm 0.61$ , and  $97.65\pm 0.76\%$  for lumefantrine at the end of 1, 3 and 6 months, respectively. It may be concluded that the liquid and S-SNEDDS of artemether and lumefantrine were successfully formulated using components which imparted higher thermodynamic stability due to its small particles size leading to higher drug release.



**Fig. 8: Cumulative drug release profiles**

*In vivo* cumulative drug release from SNEDDS (F1,  $\blacktriangle$ ), Lumither<sup>®</sup> (L-20DT<sup>®</sup>,  $\blacktriangledown$ ), pure artemether (ARTM  $\blacktriangledown$ ) or pure lumefantrine (LUMF,  $\bullet$ ) in the right panel

**TABLE 6: PHARMACOKINETIC PARAMETERS OF SNEDDS (F1), LUMITHER<sup>®</sup>, ARTEMETHER AND LUMEFANTRINE**

Formulation/drugs		Parameters			
		C <sub>max</sub> (mg/ml)	T <sub>max</sub> (h)	AUC <sub>0-72h</sub>	t <sub>1/2</sub> (h)
Artemether	Artemether	13.11±2.22	3.1±1.92	192.11±98.22	2.21±2.01
	Lumither <sup>®</sup>	110.31±40.88	92.9±1.82	390.66±132.44	2.26±1.89
	SNEDDS	110.31±40.88	2.9±1.45	598.89±114.33	2.52±1.42
Lumefantrine	Lumefantrine	2.39±1.61	6.1±1.51	68.71±18.63	114.16±2.21
	Lumither <sup>®</sup>	8.12±2.16	5.8±1.4	93.51±13.22	115.38±3.98
	SNEDDS	18.22±2.32	6.3±1.54	190.82±36.57	116.61±3.66

Mean±SD, n=5

Accurate drug loading into system imparted easy reproducibility and justified its applicability. Thus, the problem of efficiently delivering poorly water soluble drugs could be rectified by innovative lipid-based drug delivery system to increase solubility and in turn bioavailability. Hence, solid self-nano emulsifying system is a useful technology for oral delivery of artemether and lumefantrine.

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