

Original Research Article

Development and characterization of Soluplus-based solid dispersion to improve solubility

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Abstract

Purpose: To improve the solubility of lumefantrine (lum), using developed solid dispersions (SDs) with Soluplus and Kollidon VA 64, at various lum: carrier ratios to produce new-generation solid dispersions (NG.SDs).

Methods: Lumefantrine:soluplus® ratios; 1:1, 1:2, and 1:3 were employed in preparing samples B1 – B3 (2nd generation SDs), B4 – B9 (3rd generation SDs), B10 – B18 (NG.SDs). Prepared batches (B10 – B18) were characterized for loading efficiency (LE), Differential scanning calorimetry (DSC) and wide-angle x-ray diffraction (WAXRD). In vitro release was determined using USP Type I Apparatus. In vivo antimalarial study on 20 female Albino rats weighing 180 – 200 g was done by adopting Peter's four-day suppressive test, where 10 mg/kg of NG.SDs were used as test group and chloroquine tablets (CQ) were used as positive control group. Drugs were orally administered once daily for three days, and parasitemia level was assessed.

Results: Developed NG.SDs gave the highest LE of $96.70 \pm 0.12\%$ ($p < 0.05$) and the fastest drug release when compared to other generations (2nd and 3rd) of solid dispersions (samples B1 – B9). More so, DSC and WAXD of selected NG.SDs depicted broader peaks and less crystallinity when compared to pure lumefantrine ($p < 0.05$), indicating higher drug solubilization and amorphous existence in SDs. A significantly ($p < 0.05$) higher antimalarial activity (96 %) was obtained for the developed NG.SDs than physical mixture, CQ and pure lumefantrine.

Conclusion: Soluplus and Kollidon VA 64-based solid dispersion matrix is a promising approach for improving the poor aqueous solubility of Lumefantrine.

Keywords: Soluplus, Solid dispersion, Kollidon VA 64, New generation Solid dispersion, Anti-malarial

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INTRODUCTION

Developing new chemical agents (NGAs) for oral administration has been a major challenge due to

poor oral solubility problems, of which lumefantrine (lum) is no exception. Poor aqueous solubility of drugs is one of the most crucial issues in modern pharmacy. Evolution in the number of

NCA's has caused pharmaceutical researchers to face many challenges due to this issue [1,2]. This is crucial in a case of organism-related ailments causing resistance. To resolve this, some modern techniques are explored.

Solid dispersions (SDs) are among the best techniques that maintain drug molecules in a supersaturated state due to the active role played by some polymers that present the drug in either a microcrystalline state or molecular dispersion [3-6]. Solid dispersions have been reported in some studies with promising therapeutic effects [5,7]. Thus, lumefantrine SDs with Soluplus and Kollidon VA 64 are effective pharmaceutical strategy to maintain a supersaturated state. As the artemisinin-based combination therapies (ACT), which have been regarded as the best approach to tackle resistant malaria in malaria-endemic regions, are falling off their crown, it is a good idea to study how the known antimalarials could be modified to improve their bioavailability and reduce polypharmacy.

Solid dispersions approach to improve poor solubility of lumefantrine with Kolliphor HS 15, Kolliphor RH 40, and Kollidon VA 64, as drug carriers, was investigated. A similar approach has been reported [4]. Despite their functionalities, solid dispersions are not widely used in the formulations because the amorphous state may crystallize during processing (due to mechanical stress) or storage (affected by temperature and humidity changes) [8]. This limitation was equally taken care of in this work by the incorporation of Kollidon VA 64, a crystallization inhibitor [4].

EXPERIMENTAL

Materials

Lumefantrine (CAS71963-77-4 Hangzhou Dayangchem Co., Ltd, gift), Soluplus®, Kolliphor® HS 15, Kolliphor® RH 40, Kollidon® VA 64 were products of BASF, Ludwigshafen, Germany. All other reagents and solvents were of analytical grade.

Preparation of lumefantrine-based solid dispersion

The second, third, and newest-generation solid dispersion of lumefantrine was formulated using three different ratios (1:1, 1:2, and 1:3) as adopted by Ugwu *et al* [9]. Different lumefantrine: carrier ratios were weighed and mixed as presented in Table 1. Briefly, about 40 mg of lumefantrine was weighed and fixed in all the batches and then mixed at different drug : carrier ratios with an appropriate amount of Kolliphor HS 15, Kolliphor

RH 40, and Kollidon VA 64 (Table 1). In a magnetic stirrer assembly, 10 mL of methanol was used to disperse the mixed powder and stirred for 1 h. Methanol (the solvent) was allowed to evaporate, and the resulting solid mass was dried for some days in a desiccator. The fully dried lumefantrine Soluplus-based solid dispersions (LS.SDs) were pulverized in a mortar and pestle and passed through a sieve aperture of 250 µm. The sieved particles were weighed individually and then stored in air-tight containers for analysis.

Table 1: Composition of the prepared solid dispersion

Batch	L : S (mg)	K 15 (mL)	KRH (mL)	K 64 (mg)
B1	1:1			
B2	1:2			
B3	1:3			
B4	1:1	0.5		
B5	1:2	0.5		
B6	1:3	0.5		
B7	1:1		0.5	
B8	1:2		0.5	
B9	1:3		0.5	
B10	1:1		0.5	1
B11	1:2		0.5	1
B12	1:3		0.5	1
B13	1:1	0.5		1
B14	1:2	0.5		1
B15	1:3	0.5		1
B16	1:1	0.5	0.5	1
B17	1:2	0.5	0.5	1
B18	1:3	0.5	0.5	1
B19	1:1	0.5	0.5	1
B20	1:2	0.5	0.5	1
B21	1:3	0.5	0.5	1

Samples (B1 - B3), (B4 - B9), and (B10 - B18) represent 2nd, the 3rd, and the newest solid dispersion, respectively; (B19-B21) represent physical mixtures; K 15, KRH, K 64, and sL: S represent Kolliphor® HS 15; Kolliphor® RH 40; Kollidon® VA 64 and lumefantrine: soluplus® ratio, respectively

Flow properties

Bulk density of LS.SDs formulations were calculated as a ratio of the quantity to the volume occupied, while the tapped density was obtained as the ratio of the mass to occupied volume of the formulation, subsequently to tapping 500 times to achieve constant volume from a height of about 2 inches from a flat surface and calculated. Then, Hausner's ratio was computed as a proportion of the tapped density to the bulk density, while the compressibility index (%) was the proportional difference between the tapped density and the bulk density to the tapped density.

Furthermore, an earlier method was adopted in determining the flow rate and the angle of repose

of the SDs with the fixed height funnel technique [3]. The time it took the SDs to effuse via the funnel opening was recorded, and the flow rate was computed, while the height heap and the half diameter of the heap contour were measured with a rule, and the angle of repose was obtained.

Loading efficiency

About 10 mL of methanolic HCl was used to dissolve about 40 mg of the drug (lum) positioned in a beaker with continuous stirring to enhance dissolution, and the volume was made up to 100 mL mark. This solution was filtered and analyzed via a UV spectrophotometer (Spectrum lab 752, Netherlands) at 335 nm [9]. The dissolution medium was employed as a blank. The loading efficiency (LC) was calculated using the formula shown in Eq 1.

$$LC (\%) = (A/T)100 \dots\dots\dots (1)$$

Where A is the actual loading and T is the theoretical drug loading.

In vitro release study

The release rate of the lumefantrine (lum) from the optimized LS.SDs, physical, and pure drug samples were studied in simulated gastric fluid (SGF; pH 1.2) and simulated intestinal fluid (SIF; phosphate buffer; pH 6.8) as adopted by an earlier report [9]. A capsule containing a sample of 40 mg of lum was suspended in 900 mL of the biological fluid. The dissolution apparatus (magnetic stirrer) was adjusted to about 50 rpm and a temperature of $37 \pm 1^\circ\text{C}$. A 5 mL aliquot of the release medium was collected for analysis at a wavelength of 335 nm and supplemented with an equal volume at every 5 – 10 min until 60 min. This was done using the selected optimized batches.

Differential scanning calorimetry (DSC)

Thermal transitions in heat capacity of pure lumefantrine, excipients, and the lumefantrine-loaded solid dispersions (LS.SDs) were ascertained with a DSC device (Netzsch DSC 204 F1, Geratebau, GmbH, Selb, Germany). An equivalent of 2 mg of each material was weighed into an aluminium pan, hermetically sealed, and the thermal behaviour determined within the range of $20\text{--}400^\circ\text{C}$ at a heating rate of 10 K/min under a 20 mL min nitrogen flux. The thermal properties and enthalpies were noted. The crystallinity indices were also calculated (equation 2). The crystallinity index (C.I.) was used to evaluate the degree of crystallinity of the carrier matrix. This was determined from the enthalpy of the transition [4,10].

$$C.I = (EM/EC)100 \dots\dots\dots (2)$$

Where EM is the enthalpy of the carrier matrix and EC is enthalpy of the carrier

Wide-angle x-ray diffraction (WXRd)

The WXRd diffractograms of lumefantrine, B5, B17, and B20 were noted via a WXRd device (PANalytical, JB Eindhoven, Netherlands) using a copper line as a radiation source. A voltage of 40 kV, a current of 40 mA, and a scanning rate of $0.02^\circ\text{ min}^{-1}$ over a 2θ range of 3° to 40° were used as the reference standard [9].

In vivo antimalarial study

Animal

Twenty female Albino rats within the weight range of 180 – 200 g were procured from the Faculty of Veterinary Medicine, University of Nigeria, Nsukka (UNN). They were cared for and kept in standard animal cages in a conducive environment resembling their natural habitat to acclimatize for seven days with free access to food and water prior to the commencement of the experiment.

Animals were handled following the approval of the Animal Ethics Committee, UNN (approval no. FPSRE/UNN/18/00021) which complied with EU guidelines for animal experiments. The animals were randomly separated into five groups containing five rats each. Group 1 is test group treated with B18 (newest generation SDs). Group 2 is B21 (Physical mixture), group 3, chloroquine (commercial and standard sample), group 4, untreated group (negative control), and group 5, which was treated with an aqueous dispersion of pure lumefantrine. Peter's four-day suppressive test was adopted using *Plasmodium berghei* [11,12]. Malaria infection was induced by intraperitoneal (IP) inoculation of 200 μL of 1×10^6 parasitized cells/mL on day one. Animals received orally 10 mg/kg of each sample of NG.SDs, physical mixture, chloroquine tablet, and aqueous dispersion of lumefantrine powder for groups 1 – 3 and 5, respectively, 24 h after the infection was established. Dosing was done orally once daily for four days. To ascertain the parasitemia level 24 h post-treatment (day 5), two slides containing a thin blood smear obtained from the tails of the animals were prepared and stained with 10 % Giemsa in phosphate buffer (pH 7.2) for 21 min. The slide was observed via a microscope at 100x magnification. The percentage parasitemia was ascertained by calculating the parasitized red blood cells (RBC) on at least 100 RBC in random

areas of the two Giemsa-stained slides. The percentage antimalarial activity was determined as follows in Equation 3 [13].

$$\text{Activity (\%)} = 100 - (\text{MPTG/MPCG})100 \dots\dots (3)$$

Where MPTG represents the mean parasitemia of treated group and MPCG is the mean parasitemia of control group

Statistical analysis

Statistical analysis was done using GraphPad InStat Demo (USA). Data are reported as mean $\pm$ standard deviation (SD) and further analyzed with One-way analysis of variance (ANOVA). Their differences were evaluated via a two-tailed Student's T-test at $p < 0.05$, considered statistically significant.

RESULTS

Flow properties

The results of bulk density, tapped density, Carr's compressibility index, Hausner's quotient, flow rate, and angle of repose for LS.SDs as presented in Table 2 were within the ranges of 0.41 ± 0.1 - 0.44 ± 0.3 , 0.42 ± 0.2 - 0.50 ± 0.1 , $1.1 - 8.9$ %, $1.10 - 1.17$, $0.4 \pm 0.2 - 9.7 \pm 0.1$, and $38 - 50$ °, respectively.

Loading efficiency (LE)

The percentage loading efficiency (LE) results of the formulations are presented in Table 2. The

third-generation SD, sample B9 (containing drug: polymer; 1:3), showed a high LE of 84 ± 0.11 %, while the newest generation SDs (NG.SDs), B18 (containing drug: carrier 1:3), gave the highest LE of 97 ± 0.12 %. The physical mixtures, batches B19-21, exhibited significantly lower LE ($p < 0.05$) in the range of 60 - 68 % compared to the NG.SDs.

In vitro release profile of LS.SDs

In the two media, phosphate buffer, SIF (pH 6.8) and SGF (pH 1.2), the selected LS.SDs exhibited the highest dissolution rates between 20 to 60 min than the pure drug sample as presented in Figure 1 and Figure 2, respectively. The order of higher dissolution rates of the batches is $B18 > B21 >$ pure drug sample.

Differential scanning calorimetry (DSC)

DSC determinations were performed to ascertain the thermal characteristics of lumefantrine, Soluplus, Kolliphor HS 15, Kolliphor RH 40, and Kollidon VA 64 using the optimized batches of the formulations. It renders valuable information on the solid-state nature of materials. The thermograms indicated that the pure lumefantrine exhibited a sharp peak at 133.4 °C, Soluplus showed two wide endothermic peaks at 87.1 °C and artifact at 314.3 °C, Kolliphor HS 15 had a curve with a melting peak of 65.65 °C, kolliphor RH 40 showed a curve with two peaks at 84.3 °C, and artifact at 364.1 °C, Kollidon VA 64 showed a thermal peak at 319.6 °C (Fig. 3).

Table 2: Physicochemical properties of lumefantrine Soluplus-based solid dispersions

Batch	BD (g/mL)	TD (g/mL)	CI (%)	HQ	FR (g/s)	AOR (°)	LE (%)
B1	0.44 ± 0.3	0.48 ± 0.1	8.9	1.10	1.0 ± 0.1	38	47.4 ± 0.03
B2	0.44 ± 0.1	0.46 ± 0.2	3.1	1.03	1.1 ± 0.1	40	52.00 ± 0.01
B3	0.43 ± 0.2	0.45 ± 0.2	5.7	1.06	2.5 ± 0.2	38	54.60 ± 0.21
B4	0.43 ± 0.1	0.44 ± 0.3	2.7	1.03	0.9 ± 0.2	42	57.15 ± 0.10
B5	0.42 ± 0.1	0.44 ± 0.2	5.4	1.06	0.6 ± 0.3	40	64.15 ± 0.01
B6	0.42 ± 0.2	0.43 ± 0.1	2.8	1.03	0.6 ± 0.2	44	59.00 ± 0.13
B7	0.42 ± 0.2	0.46 ± 0.2	8.4	1.09	0.9 ± 0.2	44	55.20 ± 0.11
B8	0.43 ± 0.1	0.46 ± 0.2	5.7	1.06	0.6 ± 0.1	40	62.95 ± 0.10
B9	0.43 ± 0.2	0.44 ± 0.1	2.7	1.03	0.7 ± 0.2	30	84.20 ± 0.11
B10	0.43 ± 0.3	0.44 ± 0.1	2.7	1.03	0.8 ± 0.2	38	75.85 ± 0.12
B11	0.41 ± 0.2	0.42 ± 0.2	2.9	1.03	0.6 ± 0.3	34	66.65 ± 0.11
B12	0.41 ± 0.1	0.43 ± 0.2	5.6	1.06	1.1 ± 0.2	36	79.24 ± 0.10
B13	0.42 ± 0.2	0.43 ± 0.3	2.8	1.03	0.7 ± 0.1	44	67.55 ± 0.11
B14	0.43 ± 0.3	0.46 ± 0.2	5.7	1.06	0.7 ± 0.1	42	69.05 ± 0.01
B15	0.43 ± 0.2	0.47 ± 0.1	8.5	1.09	0.5 ± 0.2	46	60.40 ± 0.21
B16	0.43 ± 0.1	0.46 ± 0.2	5.7	1.06	0.9 ± 0.1	48	85.26 ± 0.11
B17	0.42 ± 0.2	0.43 ± 0.3	2.8	1.03	0.4 ± 0.2	42	81.36 ± 0.01
B18	0.41 ± 0.1	0.42 ± 0.2	1.1	1.03	1.3 ± 0.1	46	96.70 ± 0.12
B19	0.44 ± 0.2	0.50 ± 0.1	1.2	1.13	9.7 ± 0.1	56	64.60 ± 0.11
B20	0.44 ± 0.3	0.48 ± 0.2	8.9	1.09	8.8 ± 0.2	50	60.80 ± 0.10
B21	0.43 ± 0.3	0.50 ± 0.1	1.4	1.17	8.7 ± 0.3	48	67.75 ± 0.13

Values are mean $\pm$ SD; Samples (B1 - 3), (B4 - 9), and (B10 - 18) represent 2nd, 3rd, and newest solid dispersion, respectively; B19-21: physical mixtures; BD: Bulk Density; TD: Tapped Density; HQ: Hausner's Quotient; CI: Carr's Compressibility Index; FR: Flow Rate; AOR: Angle of Repose; LE: loading efficiency

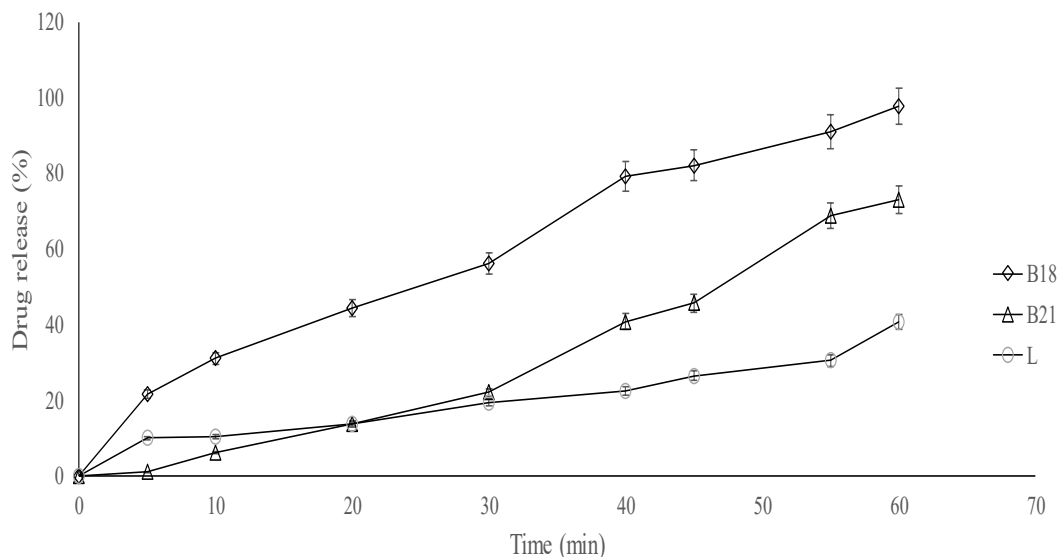


Figure 1: Drug release profile of lumefantrine in phosphate buffer (pH 6.8); B18 (newest solid dispersion); B21 (physical mixtures); L (pure lumefantrine sample)

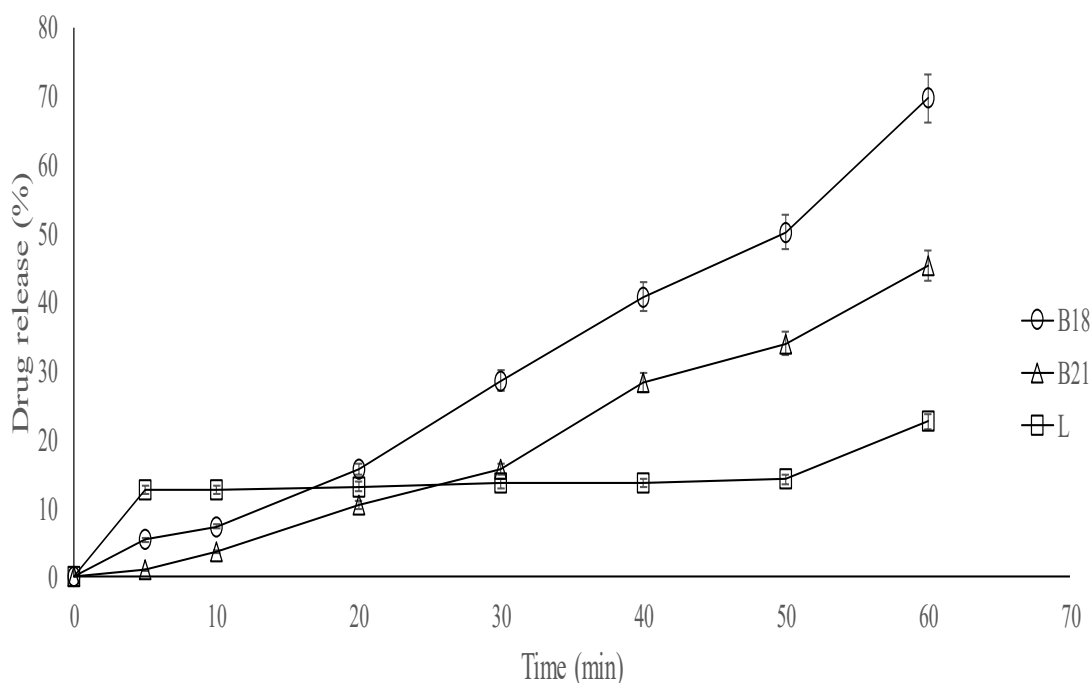


Figure 2: Drug release profile of lumefantrine in simulated gastric fluid (pH, 1.2); B18 (newest solid dispersion); B21 (physical mixtures); L (pure lumefantrine sample)

DSC curves for LS.SDs (B18, the newest generation SDs) obtained by a solvent evaporation method and B21 (the physical mixture) as in Figure 4 showed a decrease in enthalpy of lumefantrine from 133 °C to 125 °C

and 130 °C with crystallinity indices of 0.141 and 0.180, respectively.

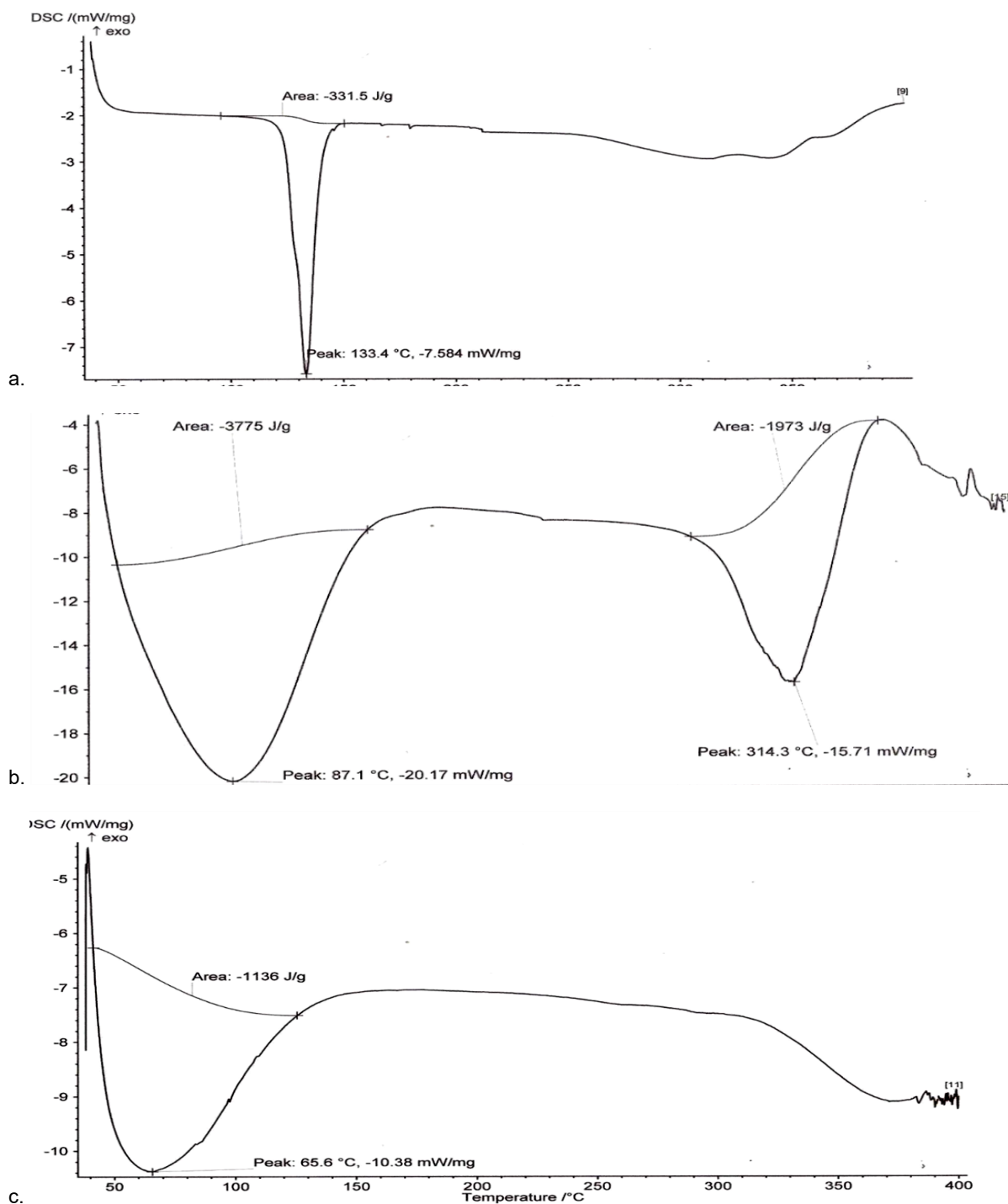
Wide-angle x-ray diffraction (WXR)

Diffractograms of lumefantrine, batch B9 (third generation SDs), while B14 and B17 (NG.SDs) are shown in Figure 5. Crystallinity of the samples is determined by the peak intensity of their diffractograms. All the SDs exhibited a similar pattern of diffractograms, indicating resemblance in their stability state.

***In vivo* antimalarial study**

The result of the antimalarial carried out as presented in Figure 6 showed the percent

antimalarial activity in the range of 90 – 95, 41 – 65, 38 – 71, and 33 - 60 % for group 1 (B18) that received new generation solid dispersions (NG.SDs), group 2 that received physical mix (B21), group 3 that received chloroquine, and group 5 that received aqueous lumefantrine, respectively. The *in vivo* antimalarial activity of NG.SDs (group 1) were significantly higher ($p < 0.05$) than other groups.



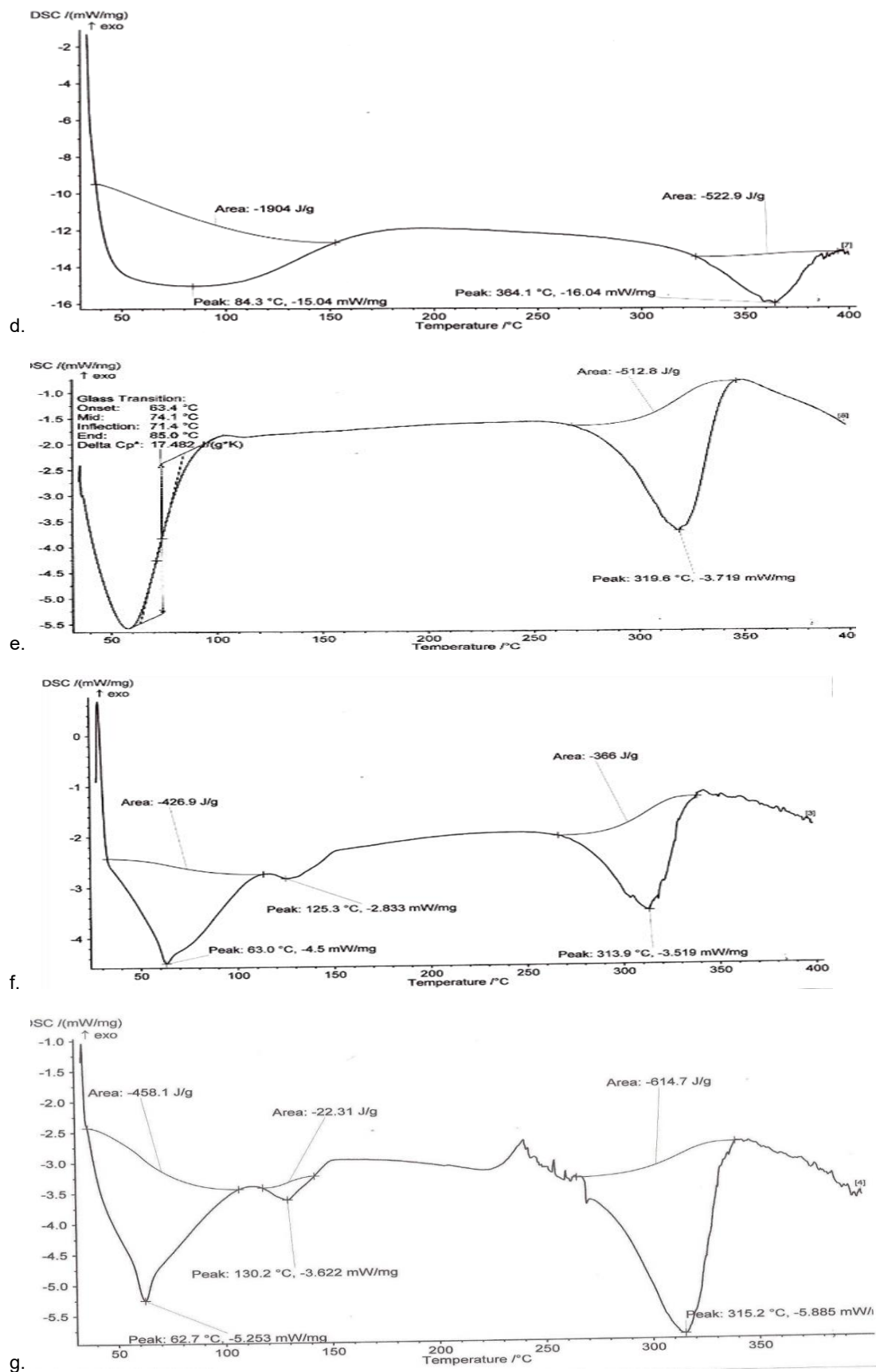


Figure 3: DSC thermogram of (a) pure lumefantrine, (b) Soluplus®, (c) Kolliphor® HS 15, (d) Kollidon® VA 64, (e) Kolliphor RH40, (f) newest solid dispersions (B18), and (g) physical mixture (B21)

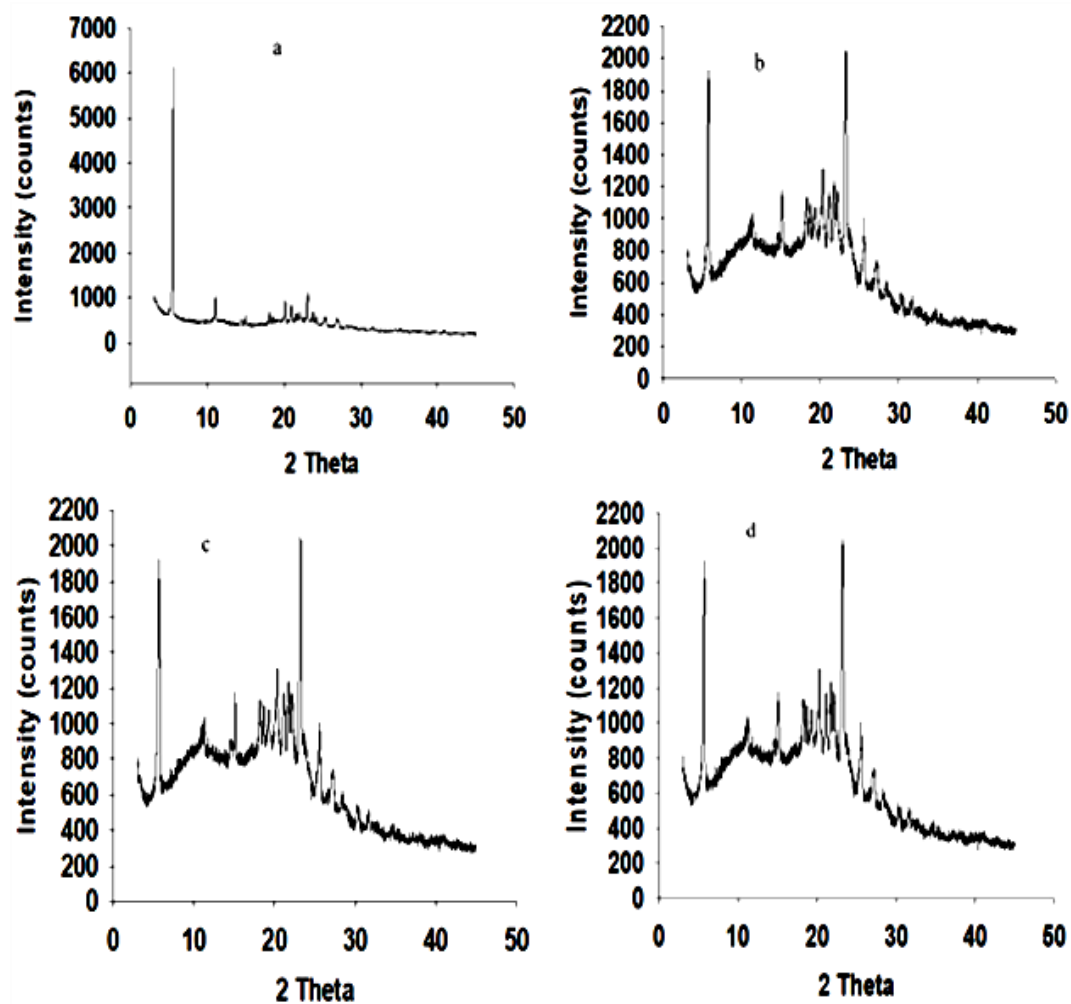


Figure 5: The WAXD diffractograms of lumefantrine (a), third generation (b) and newest generation (c and d)

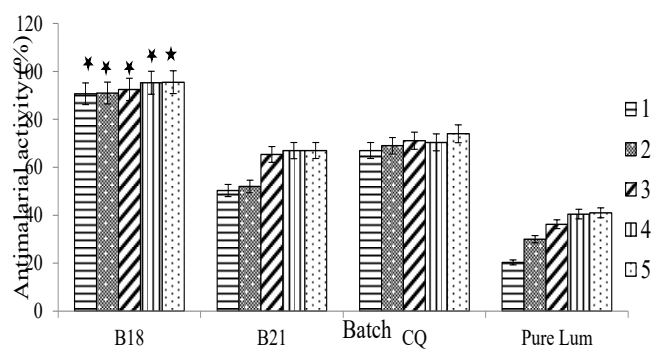


Figure 6: *In vivo* antimalarial activity of lumefantrine-based solid dispersion. *B18 (NG.SDs, $p < 0.05$, newest solid dispersion); B21 (physical mixtures); CQ (chloroquine); Pure lum (pure sample of lumefantrine); 1 - 5 (represents time intervals of 1 – 5 h duration of the experiment), $n = 5$

DISCUSSION

The different samples of LS.SDs have been shown to possess fair flow characteristics as seen in the angle of repose, though better than physical mixtures (B19 - 21). The fair flow attributes of the batches may have connections with the molecular existence of the particle sizes of matrices, carrier binding properties, and the hygroscopic nature of Kollidon® VA 64, which may introduce little agglomeration in the formulations. Therefore, these flow parameters of the formulations can be improved by the incorporation of anti-adherents if the formulations are to be formulated as capsule or tablet dosage forms to enhance the drug uniformity. In the loading efficiency, the result indicated that the sample with a higher carrier concentration in the newest generation (NG.SDs) achieved the highest LE (%). It means that Soluplus has a highly amorphous nature with enhanced solubility. Kollidon® VA 64 (crystallization inhibitor) was also present in the batch with the highest LE for better solubilization, dispersion, and crystallization inhibition of the drug [3,4,14].

The high and faster drug release was observed in LS.SDs are indicative of the effect of molecular dispersion of the lumefantrine in the carriers and decreased crystallinity of the SDs, which were enhanced by the significant presence of Soluplus, Kollidon VA 64, and other solubilizers that prevented mobilization, separation, and crystallization of saturated drug [4,11,15]. Also, from the results obtained, LS.SDs had a greater dilution potential than the pure drug sample. *In vitro* lumefantrine showed higher release in phosphate buffer (pH 6.8) than in SGF (pH 1.2). Reduced particle sizes and decreased particle aggregation contribute to enhanced drug release. More so, synergistically, Soluplus contains a carbonyl-amide group along with a hydrophobic chain that helps in interaction with hydrophobic drugs, leading to enhanced drug hydration in the aqueous fluid [16]. Soluplus and Kollidon VA 64 also contain hydrophilic chains that will improve the wettability and solubility of the drug molecule. However, the existence of pure drug sample and physical mixture (batch B21) in powder form reduced their surface areas and could also cause floating when in contact with dissolution fluids, leading to poor hydration and thus, decreased release rate. The broader endothermic peaks depicted in the SDs (LS.SDs/NG.SDs) suggest less crystallinity and an amorphous existence of the drug in SDs. This indicated the spreading of drug into the molten carriers leading to high localization and solubility of lumefantrine. The sharp peak of lumefantrine indicates a high crystallinity nature, while the broad peak of

Soluplus indicates its amorphous state and will molecularly entrap the crystalline drug creating more spaces for drug entrapment [4,17,18]. The broader peaks of LS.SDs depicted the solubilization of Soluplus into Kolliphor HS 15 and Kolliphor RH 40 which brought down their enthalpy to lower melting points significantly. Thus, Soluplus has the capacity to function as a carrier for lumefantrine.

Broad endothermic peaks were similarly observed in DSC peaks of Kolliphor HS 15 and Kolliphor RH 40 which also implied that they were more amorphous at a molecular state and would uniformly disperse lumefantrine for better solubilization in any aqueous environment. Therefore, it is important to note that the existence of SDs in an amorphous state is the best as it creates more space for the drug entrapment, enhancement of drug release, loading efficiency, absorption capacity, and above all, enhanced bioavailability. This is consistent with an earlier report [9]. On the other hand, the reduced peak intensity of the Wide-angle x-ray diffraction of SDs refers to less crystallinity of lumefantrine, which similarly confirms the acclaimed amorphous state of the SD formulations. Previous reports have shown that the amorphous state of SDs produces more spaces within the drug carrier to enhance drug entrapment, leading to improved solubility, drug release, and bioavailability [9].

The significantly high *in vivo* antimalarial activity ($p < 0.05$) observed in the newest generation SDs (batch B18) and other samples may be due to the amorphous solid dispersion formulation, which achieved molecular dispersion, good wettability, solubilization, dissolution, and better drug bioavailability.

CONCLUSION

Lumefantrine solid dispersions (LS.SDs) have been successfully prepared using a combination of Soluplus and Kollidon VA 64 by a solvent evaporation method. The newest generation solid dispersions (SDs (NG.SDs)) show the highest loading efficiency, *in vitro* and *in vivo* activity. Thus, lumefantrine Soluplus based-solid dispersion is a promising potential to achieve good drug solubility and a high amorphous state of lumefantrine for better treatment of malaria.

DECLARATIONS

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the technical staff of Pharmaceutical Technology and Industrial Pharmacy, UNN.

Ethical approval

Approval was granted by the Animal Ethics Committee, UNN (approval no. FPSRE/UNN/18/00021)

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dr. Calister E. Ugwu designed and carried out the experimental work, while Dr. Christopher E. Ugwoke read it and both approved the manuscript.

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