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Research Article

SUSTAINED RELEASE ARTEMETHER-LOADED SOLID LIPID MICROPARTICLES, BASED ON SOLIDIFIED REVERSE MICELLAR SOLUTION (SRMS)

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ABSTRACT

Objectives: To prepare and evaluate sustained release artemether-loaded SLMs based on SRMS
Material and methods: SRMS, consisting of mixtures of Phospholipon® 90H (P90H) and Softisan® 154 (1:1, 2:1 and 1:2) were formulated and characterized using differential scanning calorimetry (DSC). The SRMS were used to formulate artemether-loaded SLMs by melt homogenization. The SLMs were characterized based on particle size and morphology, pH stability, encapsulation efficiency (EE%) and loading capacity. In vitro release was carried out in simulated intestinal fluid (SIF, pH 7.5).
Results: Thermograms of the SRMS (1:1, 2:1 and 1:2) showed sharp endothermic peaks at 65.5, 64.4 and 62.3 oC respectively. Maximum EE% of 70.00 ± 1.50 % was obtained for SLMs formulated with SRMS 1:1 and 1 % artemether. Loading capacity ranged from 5.67 to 17.90 g drug/100 g lipid. In vitro release showed about 80 to 84 % drug release at 7 h. Particle size of artemether-loaded SLMs ranged from 18.60 ± 0.09 to 34.80 ± 0.30 µm. The pH decreased significantly at 60 days from 6 to 4.8 for batch A2 formulated with SRMS 2:1 and 3 % artemether ($p < 0.05$).
Conclusion: artemether-loaded SLMs based on SRMS had good sustained release properties and could be used once daily in order to enhance patient's compliance.

Keywords: Malaria, artemether, SRMS, lipids, sustained release SLMs

INTRODUCTION

Malaria remains a tremendous health burden in tropical areas causing up to 24.3 billion episodes of clinical illness and 0.86 million deaths in 2009, with annual death rates of up to 93 % of affected severe malaria [1,2]. It is a prominent parasitic life-threatening disease and accounts for 1 to 2 million deaths round the globe yearly [3]. Artemisinins are considered the keystones of the treatment of *P. falciparum* malaria due to their high potency and rapid action [4]. They have gametocytocidal properties by inhibiting parasite transmission which probably reduces the development of resistance [5]. Artemisinin is a natural anti-malarial derived from the Chinese medicinal plant *Artemisia annua* L. The artemisinins including artesunate, artemether, arteether and dihydroartemisinin are the most effective anti-malarial drugs known today and possess a remarkably wide therapeutic index [6]. They have the ability to rapidly kill a broad range of asexual parasite stages at safe concentrations that are consistently achievable through standard dosing regimens [6].

Artesunate and artemether are the two most widely used oral artemisinin derivatives. They are being used increasingly in South-east Asia and other areas of the world where multidrug resistant *Plasmodium falciparum* malaria is prevalent [7,8,9]. Both are prescribed either on their own, or, increasingly, as part of combination treatment, with the intention of providing mutual protection against resistance and enhanced efficacy. Artemether is lipophilic drug with short half life of 1.6 to 2.2 h, hence good candidate for sustained release. Due to the physicochemical and biopharmaceutical problems of artesunate such as short half-life and poor oral bioavailability, the use of this drug is now being threatened by low sensitivity of the parasites to this drug in South-East Asia and Africa [10,11,12]. Because of this challenge, there is an urgent need to develop highly efficacious formulations of artesunate to enhance their oral solubility and pharmacokinetic profiles.

The main goal of malaria therapy is to promote a high drug concentration in the intracellular parasitophorous vacuoles where the plasmodium is hosted [6]. Thus, the major setbacks of conventional malaria chemotherapy is the development of multiple drug resistance and the non-specific localization to intracellular parasites, resulting in high dose requirements and subsequent intolerable side effects which eventually lead to patient non-compliance [6,13]. Hence, to improve the delivery of anti-malarial drugs, researchers have developed and evaluated many particulate drug carriers which are mainly lipid-based (e.g. liposomes, nanoparticles, microparticles) and polymer-based (e.g. dendrimers and nanocapsules) [14].

SRMS-based carriers have been investigated, and successfully employed to achieve controlled release of drugs [15,16,17,18,19,20]. SRMS consisting of phospholipid and solid lipid (triglyceride) such as Softisan 154, a completely hydrogenated palm oil, transform into a lamellar mesophase after melting on contact with water. This transformation enables controlled release of solubilized drugs. SRMS also offer a high solubilization rate for different types of drugs [16]. The aim of the study was to formulate artemether-loaded SLMs for once daily administration in order to improve the bioavailability of the drug and at the same time inhibit resistance of plasmodium to artemether.

MATERIALS AND METHODS

Materials

The following materials were used as procured from their suppliers without further purification: Artemether (*Hangzhou Dayangchem* Co. Ltd., China), hydrochloric acid, sodium hydroxide, monobasic potassium phosphate, Tween® 80, (Merck, Darmstadt, Germany), sorbitol (Wharfedale Laboratories, Otley, West Yorkshire LS211LH, England), Softisan® 154 (Schuppen, Condea Chemie GmbH, Germany), Phospholipon® 90H (Phospholipid GmbH, Köln, Germany), distilled water (Lion water, Nsukka, Nigeria). All other reagents and solvents were analytical grade and were used as supplied.

Preparation of the lipid matrices

Mixtures of Phospholipon® 90H and Softisan® 154 (1:1, 2:1 and 1:2 w/w), were prepared by fusion. In each case the lipids were weighed using analytical balance (Adventurer, Ohaus, China), melted together and stirred at a temperature of 70 °C using a magnetic stirrer (SR1 UM 52188, Remi Equip., India), until a homogenous, transparent white melt was obtained. The homogenous mixture was stirred at room temperature until solidification to obtain the SRMS [21]

Characterisation of lipid matrices

Melting transitions and changes in heat capacity of Phospholipon® 90H, Softisan® 154 and SRMS (1:1, 2:1and 1:2) were determined using a differential scanning calorimeter (Netzsch DSC 204 F1, Geratebau, GmbH, Selb, Germany). About 10 mg of each lipid matrix was weighed into an aluminum pan, hermetically sealed and the thermal behaviour determined in the range of 20–500 °C, at a heating rate of 10 k/min under a 20 ml/min nitrogen flux. Baselines were determined using an empty pan, and all the thermograms were baseline corrected.

Formulation of the microparticles

The artemether-loaded SLMs were prepared using the melt homogenization technique [20,21] according to the formula presented in Table 1. In each case, 5 g of the lipid matrix was melted at 70 °C on a water bath and an appropriate amount of artemether was incorporated into the lipidic melt. Sorbitol was dissolved in hot distilled water at the same temperature with the lipidic melt together with Solutol® and sorbic acid. The hot aqueous phase was poured into the lipidic melt and immediately subjected to high shear homogenization with Ultra-Turrax (T25 Basic, Digital, Ika Staufen, Germany) at 5000 rpm for 10 min. SLMs containing no drug (unloaded SLMs), which served as negative control were also formulated.

Table 1: Composition of artemether-loaded SLMs

Batches	SRMS (% w/w)	Drug (% w/w)	Sorbitol (%)	Solutol® (%)	Sorbic acid (% w/w)	Distilled water q.s (ml)
A1 (1:1)	5.0	1.0	1.0	0.75	0.05	100
A2 (1:1)	5.0	3.0	1.0	0.75	0.05	100
A3 (1:1)	5.0	0.0	1.0	0.75	0.05	100
B1 (1:2)	5.0	1.0	1.0	0.75	0.05	100
B2 (1:2)	5.0	3.0	1.0	0.75	0.05	100
B3 (1:2)	5.0	0.0	1.0	0.75	0.05	100
C1 (2:1)	5.0	1.0	1.0	0.75	0.05	100
C2 (2:1)	5.0	3.0	1.0	0.75	0.05	100
C3 (2:1)	5.0	0.0	1.0	0.75	0.05	100

Batches A1 and A2 were formulated with SRMS 1:1, B1 and B2 contain SRMS 1:2 and C1 and C2 contain SRMS 2:1.

Particle size and morphology determination

The particle size of the SLMs was determined in a time dependent manner (1 day, 30 days and 90 days) by computerized image analysis of 100 microparticles. Each of the batches was placed on a microscope slide, covered with a cover slip and imaged under a binocular microscope (Lieca, Germany) attached with a Motic image analyser (Moticam, China), at a magnification of x 400. The particle morphologies were also observed and photomicrographs taken.

pH studies

The pH of dispersions of drug loaded and unloaded SLMs were determined in a time dependent manner: 1 day, 30 days and 60 days using a pH meter (pH ep® Hanna instrument, Padova, Italy) in order to ascertain if there was any form of degradation during the storage.

Determination of drug content and encapsulation efficiency

Beer's calibration curve was obtained for artemether in 1.0 N HCl at a concentration range of 0.2 to 1.0 mg% at a predetermined wavelength of 290 nm. The drug content was determined by measuring the free drug concentration in the aqueous phase. Microsphere dispersion was separated using a centrifuge (Chem. Lab. Instrument, UK) at 1,252 × g for 30 min. The obtained aqueous phase was filtered through a 0.22 µm membrane filter, diluted properly with 1.0 N HCl and analysed in spectrophotometer (UNICO 2102 PC UV/Vis Spectrophotometer, USA). The drug content was calculated with reference to Beer's calibration curve. The experiment was repeated twice and the amount of encapsulated drug was obtained by subtracting the total amount of drug per formulation from the drug concentration in the aqueous phase.

The encapsulation efficiency (EE %) of the drug in the microparticles was calculated from the equation: EE (%)= (Wi-Wf)/Wi x 100 (1)

Where Wi is the mass of drug added to the formulation, while Wf is the actual mass of drug encapsulated in the microparticles.

Drug loading capacity (LC)

LC expresses the ratio between the entrapped active pharmaceutical ingredient (API) and the total weight of the lipids [21]. LC was determined using the relationship:

$$LC = (Wa-Ws)/(Wa-Ws+Wl) \times 100 \quad (2)$$

Where Wl is the weight of lipid in the formulation, Wa is the weight of API added to the formulation and Ws is the actual amount of drug encapsulated.

In vitro release studies

The USP paddle method was adopted in this study. The dissolution medium consisted of 900 ml of freshly prepared simulated intestinal fluid (SIF pH 7.2) maintained at 37 ± 1 oC. The polycarbonate dialysis membrane (MWCO 6000-8000, Spectrum Labs, Brenda, The Netherlands) selected as release barrier was pretreated by soaking in the dissolution medium for 24 h prior to use. A quantity of SLMs equivalent to 100 mg artemether was weighed from each batch of the SLMs and placed in the polycarbonate dialysis membrane containing 2 ml of the dissolution medium, securely tied with a thermo–resistant thread and placed in the chamber of the release apparatus. The paddle was rotated at 100 rpm, and at predetermined timed intervals, 5 ml-portion of the dissolution medium was withdrawn, appropriately diluted, and analysed for drug content in a spectrophotometer (UNICO 2102 PC UV/Vis Spectrophotometer, USA) at a predetermined wavelength of 293 nm. The volume of the dissolution medium was kept constant by replacing it with 5 ml of fresh medium after each withdrawal to maintain sink condition. The amount of artemether released at each time interval was determined with reference to Beer's Plot.

In vitro release kinetics

The dissolution data for the SLMs were analyzed to determine the in vitro release kinetic mechanisms using two kinetic models including the First order, Higuchi square root equation and Ritger-Peppas empirical model as shown in Equations 3 to 5.

$$\ln Qt = \ln Q0 - K1t \quad (3)$$

$$Qt = K2t1/2 \quad (4)$$

$$Mt/M\infty = K3tn \quad (5)$$

where Qt is the amount of drug released at time t, Q0 is amount of drug released at time t = 0, k1 is first-order release rate constant, k2 is Higuchi rate constant, $Mt/M\infty$ is fraction of drug released at time t, n is diffusion exponent and is indicator of the mechanism of transport of drug through the polymer, k3 is Ritger-Peppas kinetic constant [18,19,20,22].

Statistical and data analysis

Data were analyzed using SPSS Version 16.0 (SPSS Inc. Chicago, IL.USA). All values were expressed as mean ± SD. Data were analysed

by one-way ANOVA. Differences between means were assessed using student's t-test. P < 0.05 was considered statistically significant.

RESULTS

Thermal properties of the lipid matrices

The results of thermal analysis of materials are shown in Fig.1 (a-e).

From the results, the DSC curve of Softisan® 154 (Fig. 1(a)), showed a narrow endothermic peak, with melting peak at temperature 61.4 oC. Phospholipon® 90H (Fig. 1(b)), showed a curve with the melting peak at temperature of 124 oC. Thermograms of the SRMS (1:1, 2:1 and 1:2) showed sharp endothermic peaks at 65.5 oC, 64.4 and 62.3 oCrespectively (Fig. 1(c, d, e)).

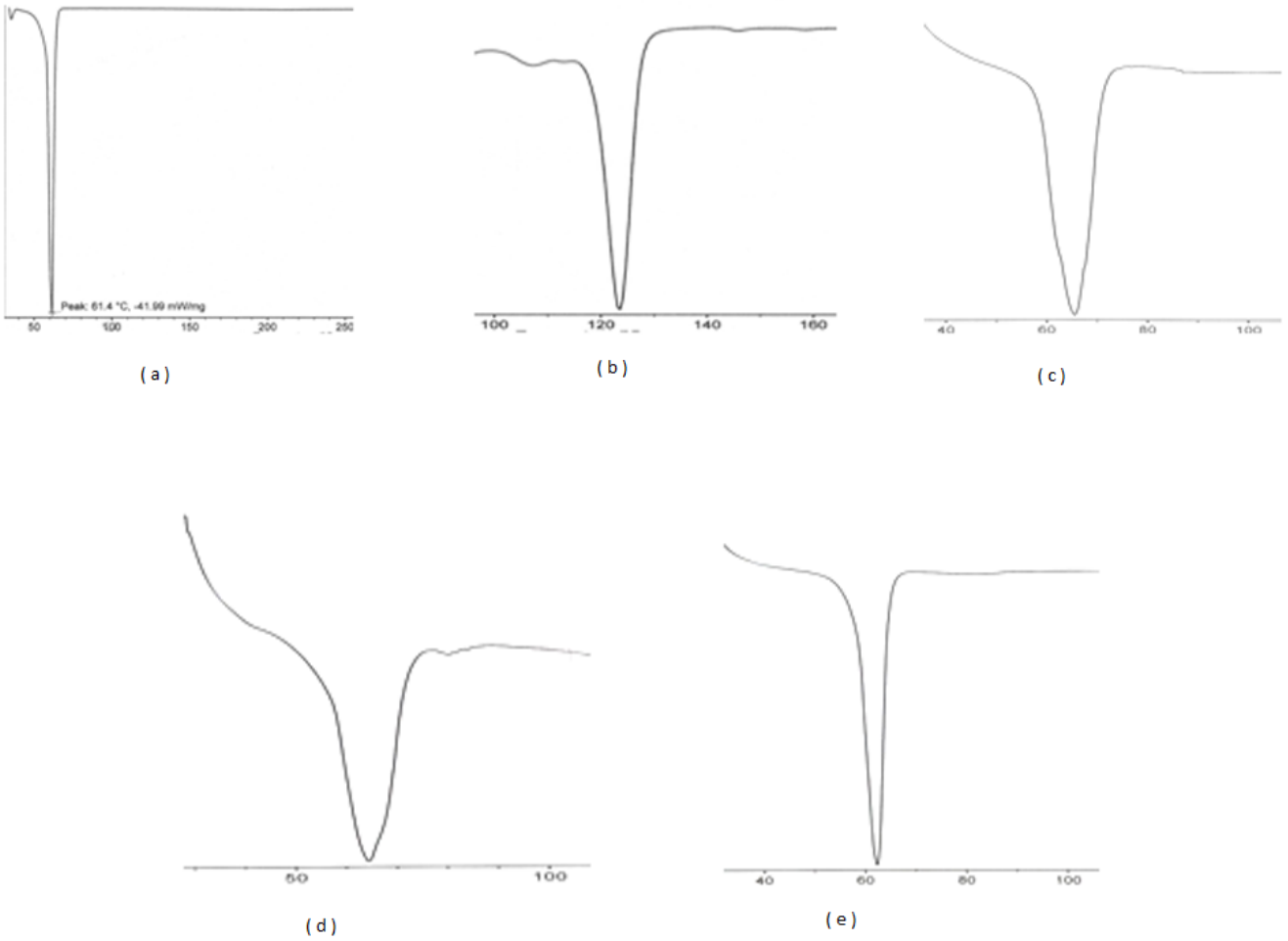

Fig. 1: DSC thermograms of: (a) Softisan® 154, (b): Phospholipon® 90H, (c): SRMS 1:1, (d): SRMS 2:1, (e): SRMS 1:2.

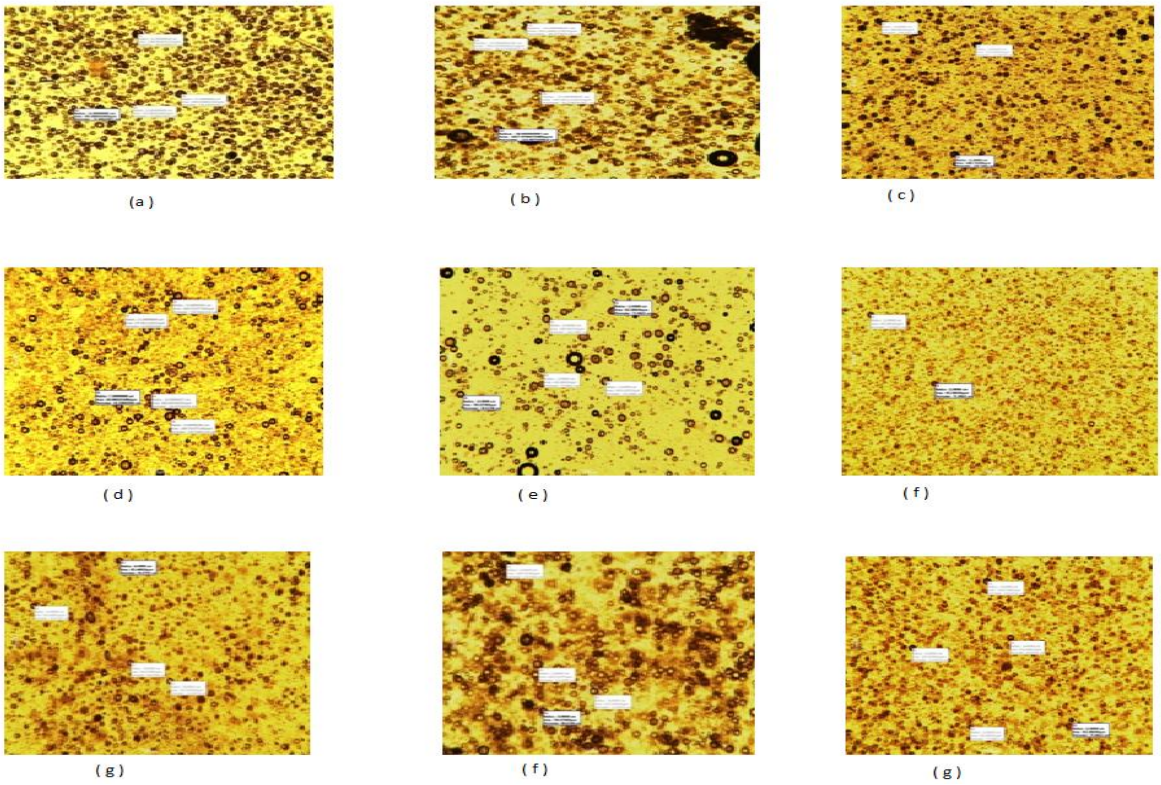

Fig. 2: Photomicrographs of solid lipid microparticles: (a): Formulated with SRMS 1:1 and loaded with 1 % artemether, (b): Formulated with SRMS 1:1 and loaded with 3 % artemether, (c): Formulated with SRMS 1:1 and loaded with 0 % drug, (d): Formulated with SRMS 1:2 and loaded with 1 % artemether, (e): Formulated with SRMS 1:2 and loaded with 3 % artemether, (f): Formulated with SRMS 1:2 and loaded with 0 % drug, (g): Formulated with SRMS 2:1 and loaded with 1 % artemether, (h): Formulated with SRMS 2:1 and loaded with 3 % artemether, (h): Formulated with SRMS 2:1 and loaded with 0 % drug.

Particle morphology and size

The results of the particle size and morphology of the SLMs are shown in Fig. 2 and Table 2. The results show that the SLMs were spherical in shape. The particle size of the unloaded SLMs were 16.40 ± 0.21, 24.20 ± 0.24 and 19.20 ± 0.23 µm for batches A3, B3 and C3 (Fig. 2 (c, f and h) respectively. However, when artemether was loaded into the SLMs there was an increase in the overall size of the SLMs across the batches as shown in **Table 2**.

Table 2: Physicochemical properties of SRMS-based artemether-loaded SLMs

Batches	Wi (%)	Wf (% ± SD)	EE (% ± SD)	Particle size (µm ± SD)	LC (g API/100 g lipid)
A1(1:1)	1.0	0.70 ± 0.22	70.00 ± 1.50	24.00 ± 0.29	5.67
A2(1:1)	3.0	1.91 ± 0.32	63.66 ± 2.52	28.80 ± 0.17	17.90
A3(1:1)	0.0	-	-	16.40 ± 0.21	-
B1(1:2)	1.0	0.49 ± 0.78	49.00 ± 3.95	28.80 ± 0.11	9.26
B2(1:2)	3.0	1.43 ± 0.34	43.50 ± 2.54	34.80 ± 0.30	23.9
B3(1:2)	0.0	-	-	24.20 ± 0.24	-
C1(2:1)	1.0	0.52 ± 0.29	52.17 ± 2.66	18.60 ± 0.09	8.76
C2(2:1)	3.0	2.10 ± 0.40	69.60 ± 1.13	32.30 ± 0.07	15.25
C3(2:1)	0.0	-	-	19.20 ± 0.23	-

Wi - mass of drug added to the formulation, while Wf is the actual mass of drug encapsulated in the microparticles, EE- Encapsulation efficiency, LC-Loading capacity; A1, A2 and A3 were formulated with SRMS 1:1, B1, B2 and B3 contain SRMS 1:2 and C1, C2 and C3 contain SRMS 2:1.

EE% and loading capacity

The results of EE% and loading capacity of SLMs are also shown in Table 2 and the results show that EE% ranged from 43.50 ± 2.54 to 70.00 ± 1.50 % and LC ranged from 5.67 to 17.90 g API/100 g lipid. Both EE% and LC increased with an increase in drug loading as shown in Table 2.

The pH stability of SLMs

The results of the time resolved pH stability of the SLMs are shown in Fig. 3. The results showed a decrease in pH over time. The pH of the SLMs ranged from 6 to 7.2 at day 1, 5.5 to 7.0 at day 7, 4.8 to 6.9 at 30 days and 3.5 to 5.3 at 60 days.

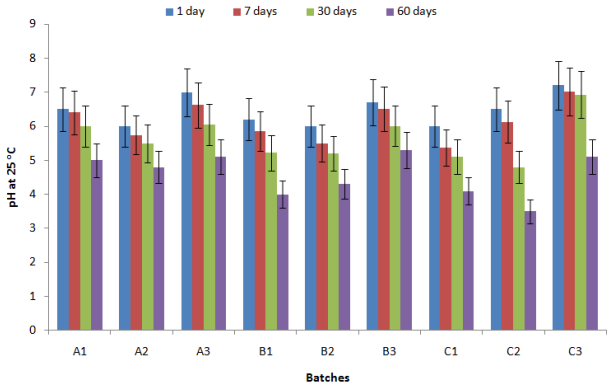

Fig. 3: Time dependent pH stability of artemether-loaded SLMs based on SRMS. Batches A1, A2 and A3 were formulated with SRMS 1:1 and contain 1, 3 and 0 % artemether, B1, B2 and B3 contain SRMS 1:2 and 1, 3 and 0 % artemether and C1, C2 and C3 contain SRMS 2:1 and 1, 3 and 0 % artemether respectively.

***In vitro* release**

The results of *in vitro* release of artemether from SLMs are shown in Fig. 4. The results revealed that artemether-loaded SLMs exhibited good sustained release properties. At T_{30} (30 min) 30.4, 36.5 and 21.7 % artemether were released from batches A1, B1 and C1 formulated with SRMS 1:1, 1:2 and 2:1 respectively and containing 1 % artemether. At T_{45} about 40, 40 and 28 % artemether were also released from batches A1, B1 and C1. At T_{240} 76, 72 and 62% artemether were released from batches A1, B1 and C1. About 80 to 84 % of artemether were released at T_{420} in all the batches as shown in Fig. 4.

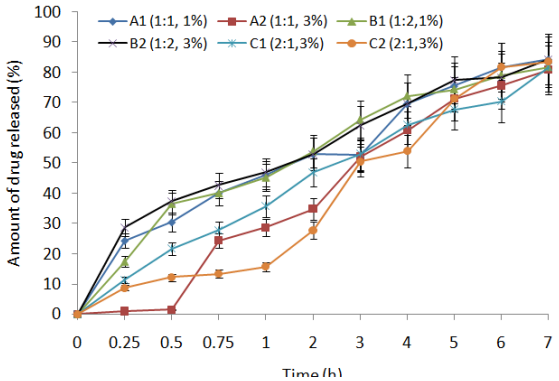

Fig. 4: Drug release profile of artemether-loaded SLMs based on SRMS. Batches A1 and A2 were formulated with SRMS 1:1, 1 and 3% artemether respectively, B1 and B2 contain SRMS 1:2 1 and 3% artemether respectively, while C1 and C2 contain SRMS 2:1, 1 and 3% artemether respectively.

***In vitro* drug release kinetics**

The results of the *in vitro* release kinetics shown in Table 3 showed that the first order kinetics model was linear with regression coefficient (r^2) range of 0.97 to 0.99. The plot of the integral form of Higuchi gave n values of < 0.5 for batches A1 and B2 formulated with SRMS 1:1 and 1:2 and containing 1 and 3% artemether respectively, while batches A2 (SRMS 1:1, 3% artemether), C1 (SRMS 2:1, 1% artemether), and C2 (SRMS 2:1, 3% artemether), gave n value > 0.5. The Ritger-Peppas model gave n value of < 0.43 for batches A1 and B2 formulated with SRMS 1:1 and 1:2 and containing 1 and 3% artemether respectively.

Table 3: *In vitro* release kinetics of artemether-loaded SLMs

Batch	First order	Higuchi		Ritger-Peppas	
	r^2	n	r^2	n	r^2
A1	0.986	0.344	0.970	0.350	0.946
A2	0.986	1.504	0.970	1.508	0.802
B1	0.968	0.452	0.955	0.474	0.891
B2	0.989	0.301	0.990	0.291	0.981
C1	0.973	0.583	0.984	0.583	0.959
C2	0.971	0.696	0.971	0.700	0.947

Batches A1 and A2 were formulated with SRMS 1:1, B1 and B2 contain SRMS 1:2 and C1 and C2 contain SRMS 2:1.

DISCUSSION

The DSC measurements were carried out in order to determine the thermal properties of Softisan® 154, Phospholipon® 90H, SRMS 1:1, 2:1 and 1:2. The narrow melting peak of Softisan®154 indicated that it is a high purity lipid. The DSC thermograms of Phospholipon® 90H revealed that it consists entirely of stable form because of the sharp melting peak seen. The DSC results of the SRMS (Fig. 1 c, d and e) showed that the structuring of Softisan® 154 with P90H generally produced matrices with lower enthalpies than the individual lipids. The results showed that SRMS 1:1, 2:1 and 1:2 generated imperfect matrices which may be due to distortion of crystal arrangement of individual lipids after melting and solidification, this may have created numerous spaces for drug localization [18,19,20]. That was the reason for low enthalpies exhibited by them. The varied fatty acid contents of these lipids may have interacted in such a manner as to partly disorder the crystal arrangement of the individual lipids [23,24,25]. Reduction in enthalpy generally suggests less crystallinity of lipid matrices which is desirable in order to achieve higher drug encapsulation efficiency [20,26,27].

The results of particle size of artemether-loaded SLMs shown in Table 2 revealed that the SLMs were within the acceptable range for microparticles. However, the particle size was affected by the ratio/combination of the two lipids used in formulating the SRMS. From the results, particle size increased with increase in drug loading in agreement with the work done by some researchers [21]. Also, the particle size of the artemether-loaded SLMs increased with increase in the amount of triglyceride (Softisan® 154) (P90H: Softisan® 154). This showed that the encapsulated drug were inside the inner core of the SLMs. The particle size however, varied significantly ($p < 0.05$) within the sub-batches and across the batches. The particle size of SLMs is important because it determines the site of administration of the drug formulations and also affects the bioavailability of formulated drug. Small particle size of liposphere (< 20 µm) is hypothesized to be well tolerated by a single cell contact, where as large particle size (> 50 µm) are much more reactive due to attractive forces (e.g. Van der waals) [28].

The results of the EE% and loading capacity also shown in Table 2 indicated that the artemether -loaded SLMs generally exhibited high encapsulation efficiencies. EE% was affected by the ratio of the two lipids used in formulating the SLMs. SRMS 1:1 (P90H: Softisan® 154) gave the highest EE% of 70.00 ± 1.50, followed by SLMs formulated with SRMS 2:1 which had EE% of 69.60 ± 1.13, while SLMs

formulated with SRMS 1:2 had EE% of 49.00 ± 3.95. The results of the LC showed that LC increased with increase in drug loading. The EE% and LC varied significantly within the batches ($p < 0.05$).

The results of the pH of both bland and artemether-loaded SLMs shown in Fig. 3 showed that the bland SLMs i.e. batches A3, B3 and C3 SLMs, formulated with SRMS 1:1, 2:1 and 1:2 (P90H: Softisan® 154) and containing no artemether exhibited an acidic pH over the study period. However, when artemether was loaded into the formulations, the pH increased to neutrality, but there were pH swings within the neutral range at day 7 and 30 days which indicated that the SLMs would require a buffer to keep a stable pH. At day 60, there was significant decrease in pH in most of the SLMs formulations ($p < 0.05$). This may be due to the release of free fatty acids by the lipids causing a decrease in pH.

The results of the *in vitro* release of artemether from the SLMs based on SRMS shown in Fig. 4 showed that drug release was affected by the ratio/combination of the SRMS used in the study. The artemether-loaded SLMs formulated with SRMS 1:2 (P90H: Softisan® 154) i.e. having higher amount of triglycerides exhibited higher initial release of the drug with up to 28 % (batch B2) of drug release at 0.25 h. This may be due to the presence of encapsulated drug in the periphery of the SLMs. However, batches A2 (SRMS 1:1, 3 % artemether), C1 and C2 formulated with SRMS 2:1 and containing 1 and 3 % artemether had lower release of drug from 0.25 h to 6 h. However, the artemether-loaded SLMs based on SRMS exhibited good sustained release of artemether over time with up to 80 % drug release at 7 h. Therefore, this formulation can be used for once daily administration of artemether in order to reduce the frequency of administration of this drug, enhance patient's compliance and increase the bioavailability of this drug.

The results of the *in vitro* release kinetics of artemether from SLMs shown in Table 3 revealed that the release kinetics followed First order and Higuchi models. The regression coefficient of the first order release was linear. The plot of the integral form of Higuchi gave n values of < 0.5 for batches A1 and B2 formulated with SRMS 1:1 and 1:2 and containing 1 and 3% artemether respectively, which showed that diffusion was the predominant mechanism of drug release, while batches A2 (SRMS 1:1, 3% artemether), C1 (SRMS 2:1, 1% artemether), and C2 (SRMS 2:1, 3% artemether), gave n value > 0.5 [29]. This showed that the drug release was by mixed mechanism i.e. not predominantly diffusion. The Ritger-Peppas model gave n value of < 0.43 for batches A1 and B2 formulated with SRMS 1:1 and 1:2 and containing 1 and 3% artemether respectively. This showed that drug release followed Fickian diffusion mechanism. However, batches A2 (SRMS 1:1, 3% artemether), C1 (SRMS 2:1, 1% artemether), and C2 (SRMS 2:1, 3% artemether), gave n value > 0.43. Therefore batches C1 and C2 followed anomalous release $0.43 < n < 0.85$ (non swellable spheres) [30], which showed that drug release was by diffusion and erosion. However, batch A2 gave non linear r^2 and n value of > 0.85.

CONCLUSION

SRMS based artemether-loaded SLMs formulated exhibited good sustained release properties for once daily administration. The SLMs showed good physicochemical properties and could be a better delivery system for artemether in order to improve patient's compliance and reduce the frequency of administration of this drug. This field however, requires further exploration in order to effectively study all its aspects and finally scale up this formulation in order to make the product available in the market.

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DECLARATION OF INTEREST

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