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Solid self-emulsifying drug delivery system for artemether with improved physicochemical properties: design and characterization

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ABSTRACT

Background: The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds.

Objectives: The purpose of this study was to formulate artemether self-emulsifying drug delivery system (SEDDS) with natural oil from sesame seeds as one of the lipidic component, transform it into powder and evaluate its potential in improving the release rate of artemether, a hydrophobic drug.

Methods: A self-emulsifying formulation of artemether composed of oil, surfactant, and co-surfactant was formulated and characterized with respect to globule size, polydispersity index (PDI), emulsification time, ingredients compatibility and stability. The formulation was converted to powder by adsorption on Aerosil®, evaluated for flow and surface morphology using a scanning electron microscope. The formulation *in vitro* drug release was determined and compared with a marketed product.

Results: The formulation was stable, showed excellent emulsification time of 6.0 s, had a mean globule size of 33.59 nm and PDI of 0.182. Direct incorporation of artemether-SEDDS into Aerosil® at a ratio of 2:1 $^{w}/_{w}$ (artemether-SEDDS: Aerosil®) resulted in a dry powder with good flow according to the Carr's scale, with a mean particle size of 268.33µm, which were mostly spherical, with highly rough and porous surfaces. At 30 min, the marketed formulation released 46 % drug lower than the solidify artemether-SEDDS

Conclusion: The study substantiates the usefulness of SEDDS for overcoming some of the physicochemical challenges associated with the delivery of artemether.

Keywords: artemether, antimalarial, globule size, solubility, sesame oil, formulation

Système d'administration de médicament auto-émulsifiant solide pour artéméther avec des propriétés physicochimiques améliorées : conception et caractérisation

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RESUME

Contexte: L'administration orale de médicaments hydrophobes présente un défi majeur en raison de la faible solubilité aqueuse de ces composés.

Objectifs: Le but de cette étude est de formuler le système d'administration de médicament auto-émulsifiant artéméther (SEDDS) avec de l'huile naturelle de graines de sésame comme l'un des composants lipidiques, de la transformer en poudre et d'évaluer son potentiel dans l'amélioration du taux de libération de l'artéméther, un médicament hydrophobe.

Méthodes: Une formulation auto-émulsifiante d'artéméther composée d'huile, de surfactant et de co-surfactant a été formulée et caractérisée en ce qui concerne la taille des globules, l'indice de polydispersité (PDI), le temps d'émulsification, la compatibilité et la stabilité des ingrédients. La formulation a été convertie en poudre par adsorption sur Aerosil®, évaluée pour la morphologie de l'écoulement et de la surface à l'aide d'un microscope électronique à balayage. La formulation de libération *in vitro* de médicament a été déterminée et comparée à un produit commercialisé.

Résultats: La formulation était stable, présentant un excellent temps d'émulsification de 6,0 s, avait une taille moyenne de globule de 33,59 nm et un PDI de 0,182. L'incorporation directe d'artemether-SEDDS dansAerosil® dans un rapport de 2:1 $^{w}/_{w}$(artemether-SEDDS: Aerosil®) a donné lieu à une poudre sèche avec un bon écoulement selon l'échelle de Carr, avec une taille moyenne de particules de 268,33µm, qui étaient principalement sphériques, avec des surfaces très rugueuses et poreuses. À 30 minutes, la formulation commercialisée a libéré 46% de médicament en moins que le solidifyartemether-SEDDS

Conclusion: L'étude corrobore l'utilité du SEDDS pour surmonter certains des défis physicochimiques associés à la livraison de l'artéméther.

Mots-clés: artemether, antipaludique, taille de globule, solubilité, huile de sésame, formulation

INTRODUCTION

Despite the fact that we live in an era of advance technology and innovation, infectious diseases like malaria, continue to be one of the greatest health challenges worldwide.[1] According to the World Health Organization (WHO)[2], malaria is now the fourth highest cause of death, accounting for 10% of children mortality in sub-Saharan Africa. It constitutes a major public Health problem in about 95 countries of the world, affecting about 40% of the world's population and the WHO estimated that there were 216 million documented cases of malaria in 2016 which resulted in the death of about 445,000 people.[3] Although it is evident that some reductions in malaria – related mortalities have been recorded,[4] there is continuous threat of antimalarial drug resistance and its spread as there are recent reports of parasite resistance to currently used antimalarials in some malaria endemic areas.[5-7] The malaria parasite, *Plasmodium falciparum* is the most deadly of all the malaria causing Plasmodium species and causes deadly forms of malaria, especially in individuals with low immunity to the disease.[8-10] Untreated malaria in such individuals after the onset of fever rapidly develops into cerebral malaria, neurological deficit and death. Malaria in pregnancy still remains a major cause of maternal death, abortion, stillbirth, premature delivery and low birth weight.[10, 11] *Plasmodium falciparum* developed resistance to relatively cheap antimalarials such as chloroquine, sulphadoxine, pyrimethamine and it became necessary to adopt the artemisinin-based derivatives and their combinations with other antimalarial drug classes for malaria therapy. Although this has recorded significant success in the fight against malaria, there are increasing reports of parasite resistance to the artemisinin-based combinations in some areas of high transmission and drug burden.[10] Artemether, a semi-synthetic derivative of artemisinin extracted from the plant *Artemisia annua* is primarily used for the treatment and management of malarial infections. However, the therapeutic potentials of artemether is considerably hampered due to its low oral bioavailability (approximately 40%) which stems from it poor aqueous solubility.[12] In the face of this challenge and with limited drug options, it is important to search for effective alternatives. This scenario has enforced the smart and effective utilization of the current antimalarial agents with the help of novel drug delivery systems. Researchers have explored different novel approaches such as, micronization, solid dispersions, inclusion complexes, complexation with hydrophilic polymers, supersaturable systems, liposomes and dendrimers or different routes such as transdermal and rectal routes with the objective to improve the efficacy of artemether.[12, 13, 14] Although these approaches have shown some level of success to improve the efficacy of the antimalarial agent, none is considered to be highly satisfactory due to problems such as high cost of manufacture (in case of supersaturable systems and liposomes), high cost of excipients (in case of liposomes), difficulty in industrial scale up (in case of dendrimers) and patient non-compliance (in case of rectal route).

The self-emulsifying drug delivery systems (SEDDS) have gained a great interest as a commercially feasible novel lipid-based delivery system and they have shown capability to improve oral bioavailability and therapeutic efficacy of several therapeutic agents.[12,15,16] A commercially available SEDDS preparation is Neoral® (cyclosporine A). SEDDS are composed of a mixture of oil, surfactant, cosurfactant and drug. They form fine oil-inwater emulsions when introduced into aqueous media under mild agitation. The digestive motility of the stomach and intestine provides the agitation necessary for self-emulsification *in vivo*.[17] SEDDS typically produce emulsions with smaller droplet (< 50nm) and are able to present and maintain the drug in dissolved state all over its transit through the gastrointestinal tract.[18] The smaller oil droplets provide a large interfacial area for pancreatic lipase to hydrolyze triglycerides and thereby promote the rapid release of the drug or formation of mixed micelles of the bile salts containing the drug.[17] The surfactants used in SEDDS are known to improve the bioavailability by various mechanisms including: (a) improved drug dissolution;[19] (b) increased intestinal epithelial permeability;[20] (c) increased tight junction permeability;[21] and (d) decreased/inhibited p-glycoprotein drug efflux.[15,17]

Most SEDDS are liquid or semisolid at room temperature and require encapsulation or solidification to facilitate ease of dosing. Solidification is typically achieved by either combination with carriers or additives to form powders or by the use of high melting lipids to generate semi-solid or solid formulations that may be encapsulated or processed to form lipid-based multiparticulates.[15] Adsorption onto solid carriers, spray drying, melt granulation, melt extrusion, freeze drying and solvent evaporation have all been used to convert

lipid-based formulations (LBF) to solid forms and have been well described in recent reviews.[22] Solid selfemulsifying drug delivery systems have exhibited more

commercial potential and patient acceptability as compared to the liquids.[12, 23]

The objective of this study was, to formulate artemether SEDDS with natural oil from sesame seeds as one of the lipidic component, transform it into powder and evaluate its potential in improving the release rate of artemether. The natural sesame oil used in this study has been evaluated as a basis for drug delivery.[14]

METHODS

Artemether powder obtained from Afrab Chem. Nigeria Ltd, Lagos. Un-refined natural sesame oil obtained from pressed sesame seeds from Altine Oil, Nigeria. Cremophor EL (polyoxyl-35-castor oil) from BASF India Ltd. Labrafac CC (caprylic/capric glycerides) and Polyethylene glycol-400 (PEG-400) from BDH Chemicals Ltd, Poole England. Silicon dioxide (Aerosil® 200 pharma) from Evonik industries AG, Germany. All other materials and chemicals used were of analytical reagent grade and were used as received.

Preparation of Artemether-SEDDS

In a previous work,[24] we studied the phase behaviour of a mixture composed of oil (1:1 mixture of natural sesame oil and labrafac CC), surfactant (Cremophor EL) and cosurfactant (Polyethylene glycol-400) and investigated its pseudoternary phase diagram to identify the rational combination of excipients which will help in developing an impeccable formulation with robust performance. Through the pseudoternary phase diagram investigation, an optimal SEDDS mixture (Table 1) was selected and artemether was incorporated for *in vitro* evaluation. Preparation of artemether SEDDS was simply through mixing the components. Artemether was dispersed into the mixture of oil and surfactant-co-surfactant mix (selected from the pseudo-ternary phase diagram) with constant stirring and was kept at 50 - 60 °C for 10 min to obtain a good blend of oil-surfactant mixture in a liquid state. The mixture was cooled to ambient temperature, sealed in a glass vial, stored for 3 months and observed for drug precipitation or changes in organoleptic properties.

Table 1: Relative composition of the optimal artemether-SEDDS formulation

Drug/Excipient	Composition (mg)	Function
Artemether	20	Active pharmaceutical ingredient
Natural sesame oil + labrafac CC (1:1)	75	Oil
Cremophor EL	140	Surfactant
PEG- 400	35	-Cosurfactant
Total	**270**	

Determination of emulsification time

One mL of the mixture was added to 200 mL of distilled water, maintained at 37 ± 2 °C under continuous stirring at 50 rpm. The time taken to obtain a uniform cloudy/turbid dispersion was recorded as the emulsification time.

Determination of globule size and polydispersity index

One mL of the formulation was diluted with distilled water to 100 mL in a volumetric flask. The flask was inverted and shaken gently to mix thoroughly. The globule size (Z) and polydispersity index (PDI) of the resultant emulsions was determined by dynamic light scattering technique using Malvern Zetasizer ZS90 (M/s Malvern Instruments, Worcestershire, UK).

Stability and compatibility studies

The formulation was stored for 6 weeks under refrigeration (4 - 8 ± 2 °C), ambient room temperature (27 - 30 ± 2 °C), elevated temperature (45 ± 2 °C) and evaluated for drug content. It was also subjected to a 24 hour cycle of refrigeration and alternate storage at ambient laboratory temperature for one week and observed for phase separation or drug precipitation The infrared spectra of freshly prepared and 6 weeks old samples stored at room temperature (28 ± 2 °C) were taken over the range 650 - 4,000 cm^{-1} and examined for shifting of peaks to either higher or lower frequencies, disappearance or appearance of new bands to determine any possible interaction.

Formulation of solid artemether SEDDS

Based on a preliminary evaluation of SEDDS adsorption, silicon dioxide was chosen as the solid adsorbents to load the artemether-SEDDS. The artemether-SEDDS was added in increments to the adsorbent and blended in a mortar to give a free-flowing powdered mixture. The flow behaviour of the artemether-SEDDS powder, the particle size, angle of repose, bulk and tapped densities were determined.

Release rate determination

The equivalent of 20 mg of artemether standard (filled into a dialysis bag), liquid artemether-SEDDS (filled into a dialysis bag), artemether-SEDDS powder (filled into a size '0' hard gelatin capsule) and a marketed formulation containing 20 mg artemether were subjected to drug release studies in 500 mL of simulated gastric fluid (SGF) without pepsin (pH 1.2) for 1 h at 37 ± 2 °C and a rotation speed of 100 rpm using the USP paddle method. Aliquot portions (5 mL) were withdrawn at predetermined intervals, namely 5, 10, 15, 20, 30, 40, 50 and 60 min, followed by replenishment with equal volumes of fresh dissolution medium. The withdrawn samples were filtered, diluted appropriately with 1 M methanolic HCl, heated at 60 ± 2 °C for 3 h (for artemether derivatization), cooled to room temperature and analyzed using UV spectrophotometer (WWR UV- 6300PC double beam, Switzerland) at wavelength of 254 nm.

Data analysis

The data generated from the various determinations were analyzed using SPSS 23 software (SPSS, Chicago, IL, USA) and are presented as the mean ± standard deviation (SD). The differences between the data sets were determined using t-test and $p < 0.05$ was considered statistically significant.

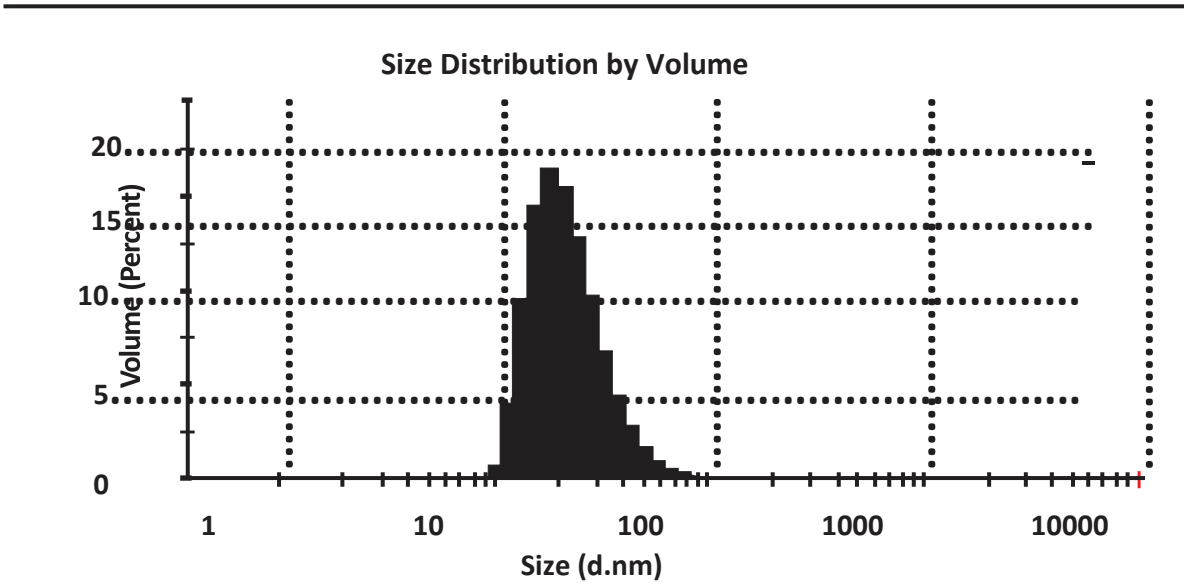

Figure 1: Graphical presentation of globule size (Z) and polydispersity index (PDI) of the prepared artemether-SEDDS

RESULTS

Emulsification time, phase separation, drug precipitation, globule size and polydispersity index.

The emulsification time of the prepared artemetherSEDDS was 6 s. No drug precipitation or changes in organoleptic properties was observed after storage at ambient temperature for 3 months. The result of mean globule size and polydispersity index determination is provided in Figure 1. The formulation had a mean globule size of 33.59 and a PDI of 0.182.

Size (d.n...	% Volume:	St Dev (d.n...
23.24	100.0	10.43
0.000	0.0	0.000
0.000	0.0	0.000

Stability and compatibility studies

Table 2 gives the results of drug content determination of artemether-SEDDS after six weeks of storage at refrigeration (4-8 ± 2 °C), room temperature (27-30 ± 2 °C) and elevated temperature (45 ± 2 °C). During the 6 weeks of stability study, no change in color or appearance under all storage conditions was observed. There was however, a decrease in drug content from 94.0 to 93.0 % for the sample stored at 45 °C.

The FT-IR spectra of day one (1) and six weeks (6) old formulations are presented in Figure 2. The characteristic FT-IR peaks for artemether and artemether + excipients occurred at 1690-1760 cm^{-1} due to C=O stretching and 1060-1150 cm^{-1} indicating C-O stretching.

Table 2: Results of drug content assessment of the freshly prepared and six (6) weeks old artemether-SEDDS

	Percentage drug content			
	Day 1	Week 6	*P*-value	Temperature
Refrigeration (4-8 ± 2 °C)	94.0±1.42	94.0±0.89	1	
Room temperature (27-30 ± 2 °C)	94.0±0.89	94.0±0.00	1	
Elevated temperature (45 ± 2 °C)	94.0±1.15	93.0±0.62	0.118	

If P-value<0.05, then there exist a significant difference at 5% level of error

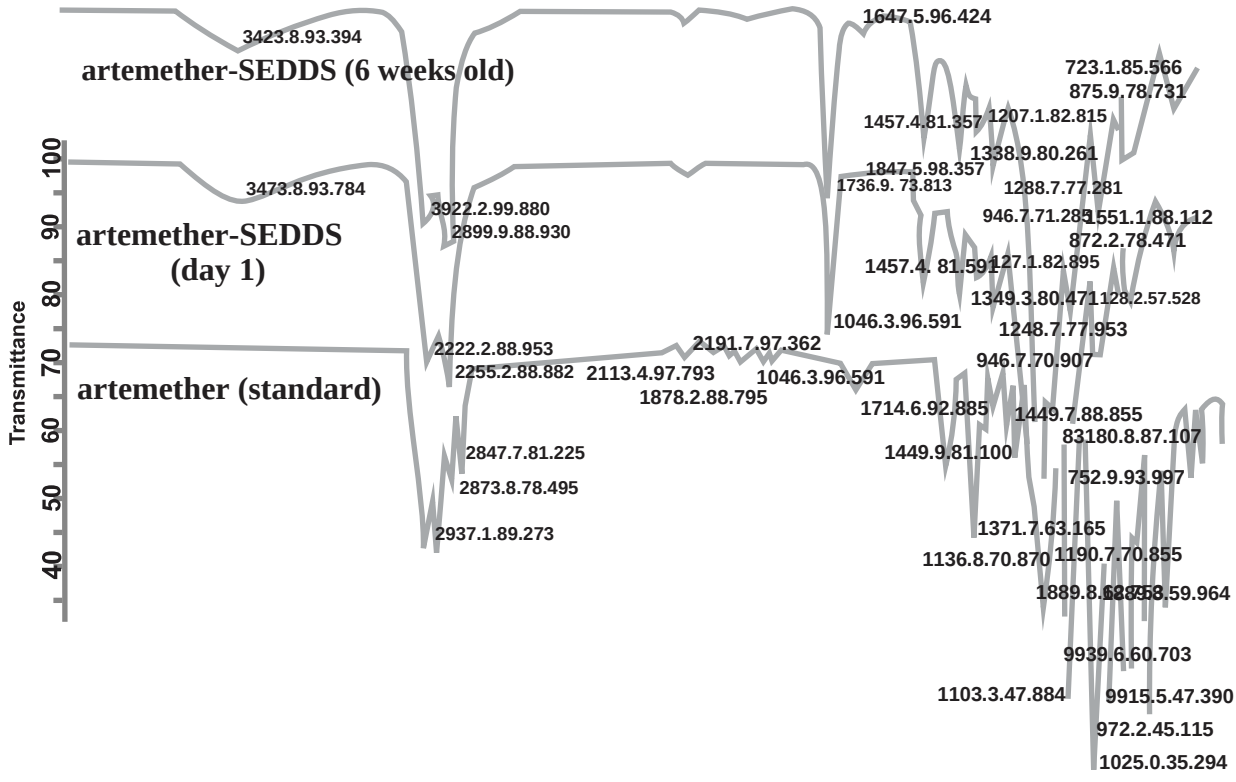

Figure 2: FT-IR spectra of pure artemether, day one (1) and six weeks (6) old artemetherSEDDS superimposed for comparison

Micromeritic properties of the artemether-SEDDS powder

The artemether-SEDDS powder had a Carr's index, Hausner ratio and angle of repose of 12.5, 1.14 and 31.5 respectively. About 32 % of the powder's particles were between 450 to 900 µm, while 17 % were less than 154 µm. The mean particle size was 268.33µm. Figure 3 shows the particle size distribution of the artemether-SEDDS powder. The scanning electron microscope (SEM) investigation revealed that the particles were mostly spherical, with highly rough and porous surfaces as shown in Figure 4.

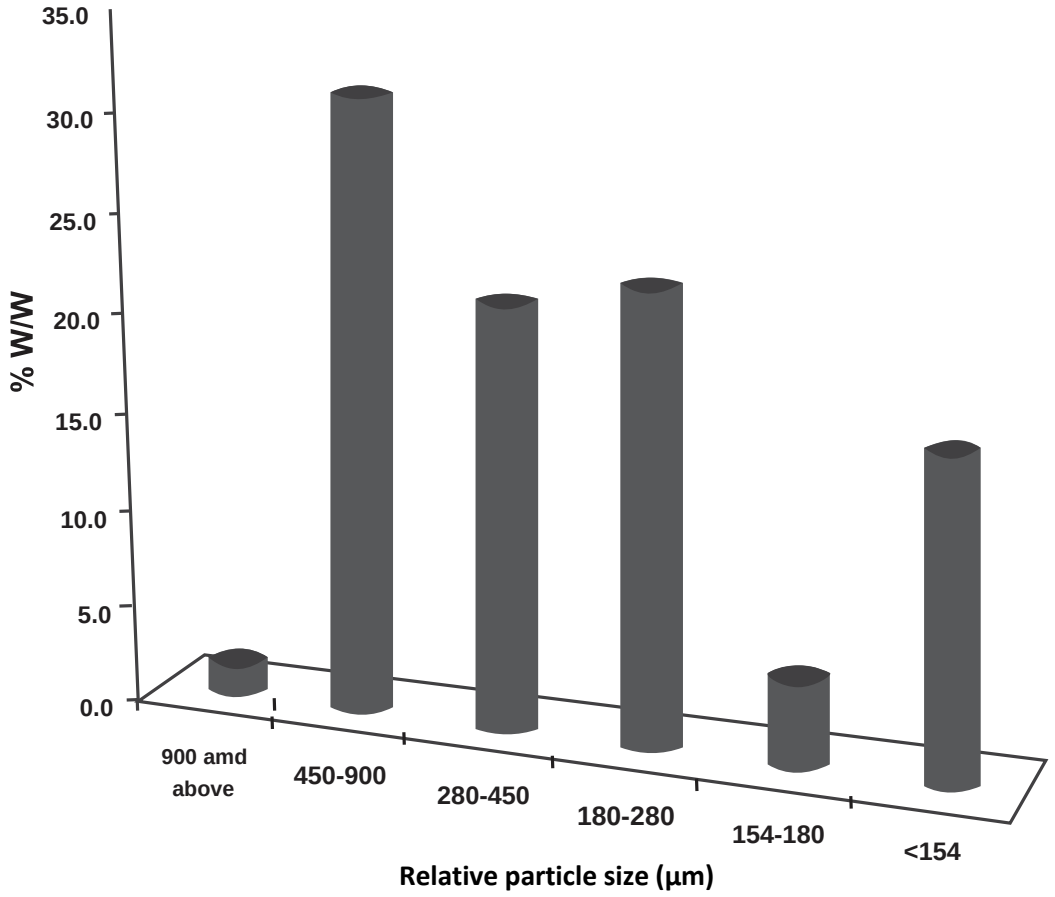

Figure 3: Particle size distribution of artemether-SEDDS powder

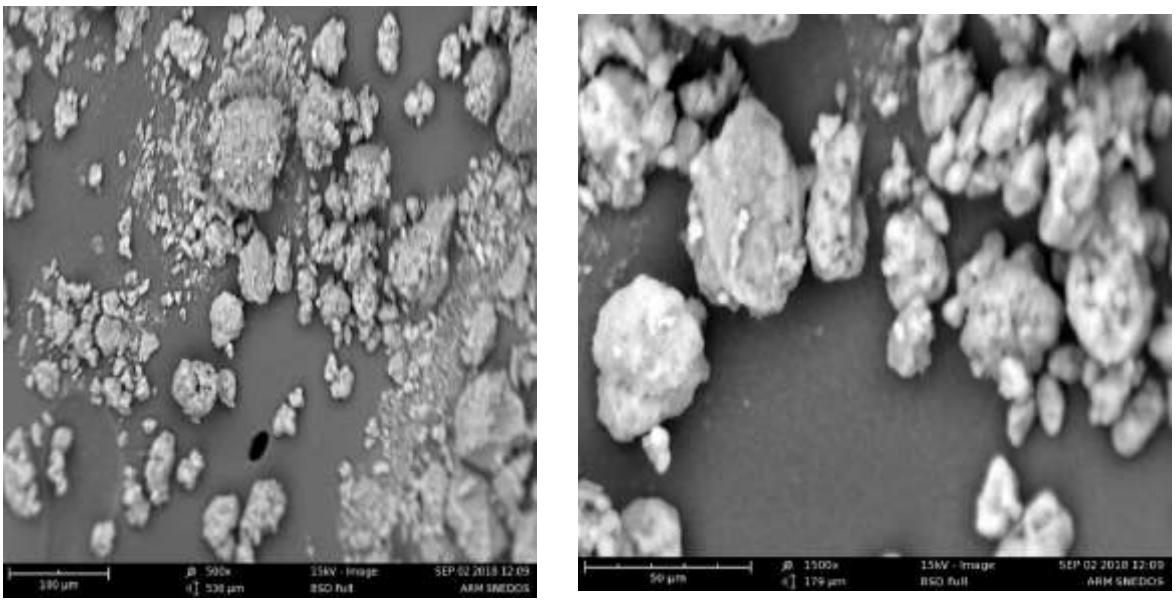

Figure 4: SEM photomicrograph of artemether-SEDDS powder left (500x), right (1500x)

In vitro release profiles of artemether formulations Figure 5 shows the drug release profile of pure artemether, liquid artemether-SEDDS, artemetherSEDDS powder and the marketed formulation. The liquid artemether-SEDDS released over 97 % of the drug within 20 min while the artemether SEDDS powder required 30 min to release over 95 % of the drug. The pure drug and marketed formulation released only 19.7 and 76 % drug respectively over a period of 60 min. The release rate was in the order of liquid formulations > solidified formulations > pure artemether (standard).

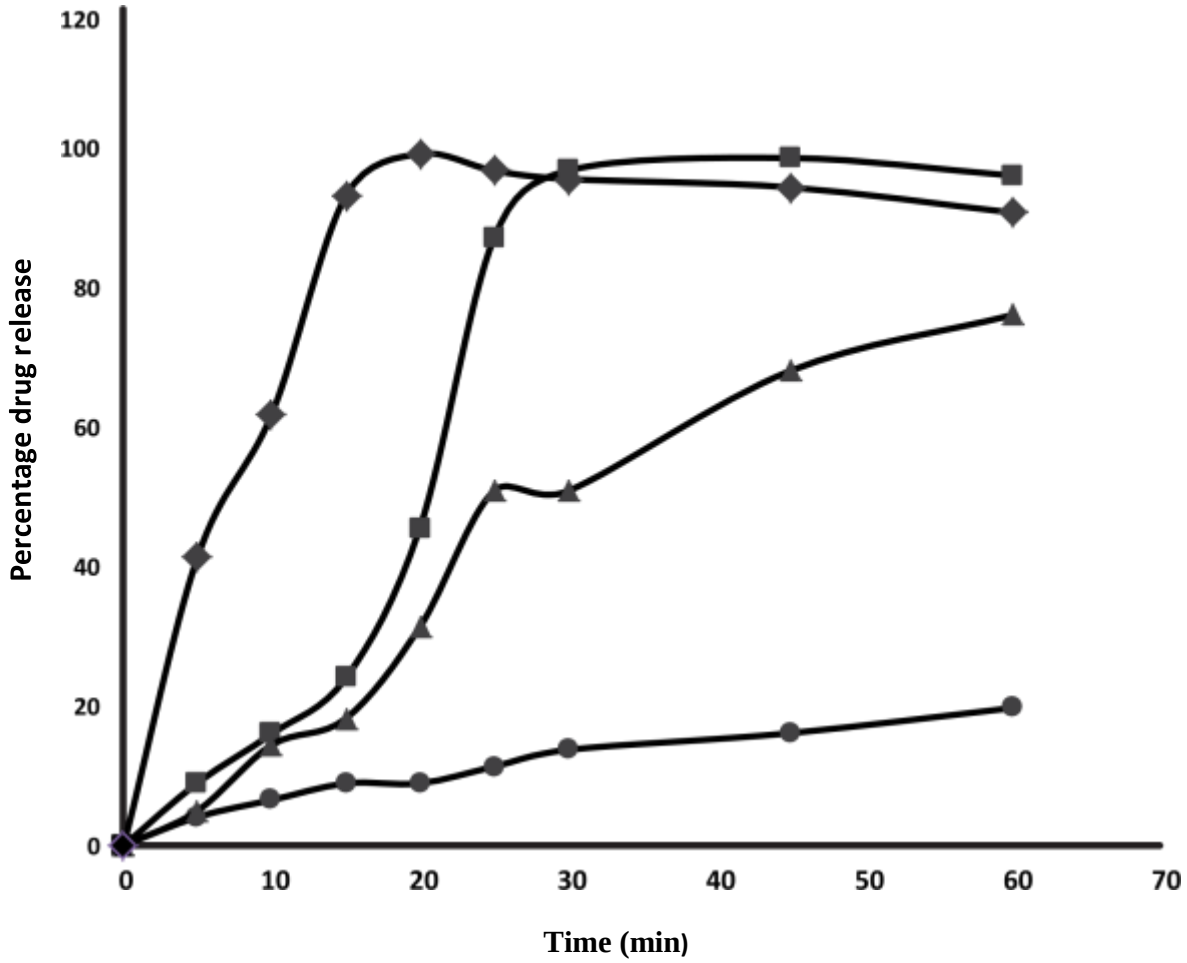

Figure 5: Percent drug released from (●) pure artemether, (▲) Marketed formulation (■) artemether -SEDDS powder and (♦) liquid artemether

DISCUSSION

Self-emulsification has been shown to be specific to the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; only very specific pharmaceutical excipient combinations could lead to efficient self-emulsifying systems.[25] The formation of micro/nanoemulsion from self-emulsifying formulations is a spontaneous process. The speed of emulsification is an important pointer for assessing the efficacy of emulsification.[16] The low self-emulsification time (6 s) indicates that when dispersed in aqueous media under mild agitation the formulations will rapidly form fine oilin-water emulsions. The result is consistent with the findings of Yahaya *et al*., [14] who reported an emulsification time of less than 10 s for a self-emulsifying formulation containing sesame oil as the lipidic carrier. The digestive motility of the stomach and intestine is expected to provide the agitation necessary for self-emulsification *in vivo*.[14, 26]

Droplet size distribution following self-emulsification is a critical factor to evaluate a self-emulsifying drug delivery system. It shows the quality of the emulsion formed.[27] Small droplet size indicate an effective emulsification system, it also reflects the formation of a better closepacked film of the surfactant at the oil-water interface, thereby stabilizing the oil droplets.[14, 26, 27, 28] Upon selfemulsification, the formulation yielded an emulsion with a mean globule size of 33.59 nm and a PDI of 0.182. This compares well with the report of Yahaya *et al*.,[24] who reported a mean globule size of 32.0 nm for piroxicamSEDDS formulated using similar lipidic constituents (a mixture of sesame oil and caprylic/capric glycerides). The smaller globule size was attributed to the relatively shorter chain length triglyceride content of caprylic/capric glycerides. Oils consisting of shorter chain triglycerides have low viscosity, which is known to increase the spontaneity of emulsification, hence, improving the emulsification efficiency which in turn impact positively on the emulsion globule size.[29] Globule size is thought to have an effect on drug absorption, the smaller the globule size, the larger the interfacial surface area for drug absorption.[24, 26] The polydispersity index depicts the degree of uniformity in globule size within a formulation. The higher the polydispersity index (PDI), the lower the uniformity of the globule sizes in the formulation.[24, 26]

Temperature fluctuation/cycling potentially accelerates physical deterioration of the product, it encourage particle growth in suspensions; cracking of emulsions, and precipitation of dissolved drug from solutions. In tropical regions where oral liquid dosage forms require refrigeration after opening, evaluation of their response to periodic alternate refrigeration and ambient temperature conditions is imperative to justify their stability. Such studies also allow the effect of extreme temperature variations during distribution of the product to be evaluated[30-33]. The absence of phase separation or drug precipitation during the 24 hour alternate refrigeration/laboratory temperature cycles indicates that the formulation is stable. Also, during the 6 weeks of stability study, none of the stored samples showed any change in any of the physical parameters - phase separation, drug precipitation, appearance and smell under all storage conditions. There was no significant difference ($P > 0.05$) in the drug content between the freshly prepared (day 1) and six weeks old samples stored under freezing and ambient temperature indicating that the formulation is stable. There was however a 1 % decrease (though not statistically significant, *$P > 0.05$)* in the drug content of the freshly prepared and the six weeks old samples stored at elevated temperature (45 ^{o}C). This could be attributed to the fact that at high temperatures, rapid chemical degradation which may not be significant at Analysis of the FT-IR spectra indicated that there was no formation of new peaks, no disappearance of old peaks or shifting of their positions, indicating the absence of chemical interaction between the formulation components thereby confirming that the formulation is stable and its components compatible.[34]

The dimensions of a particulate solid are important in achieving optimum production of efficacious medicines. Particles size influences the production of formulated medicines as solid dosage forms. Both tablets and capsules are produced using equipment that controls the mass of drug and other particles by volumetric filling. Therefore, any interference with the uniformity of fill volumes may alter the mass of drug incorporated into the tablet or capsule and hence reduce the content uniformity of the medicine.[35] Direct incorporation of artemether-SEDDS into Aerosil® at a ratio of about 2:1 $^{w}/_{w}$ (artemether-SEDDS: Aerosil®) using a solvent-free method resulted in a dry powder. The mean particle size of the adsorbed SEDDS was 268.3 µm, particles larger than 250 µm are usually relatively free-flowing but as the size falls below 100 µm, powders become cohesive and flow problems are likely to occur.[35] The flowability of powder is of critical importance in the production of tablets and capsules, free flowing powders give uniform tablets and capsules weight and content uniformity.[36] Based on the result obtained (Carr's index of 12.5, Hausner ratio of 1.14 and angle of repose of 31.5), the artemether-SEDDS powder had good flow according to the Carr's scale, 37. Obitte *et al*., [37] equally reported a good flow rate of SEDDS preparation adsorbed onto magnesium aluminum metasilicate at a ratio of 1:1 w/w without the inclusion of popular flow aids (lubricant and/or anti-adherent).

Comparative evaluation of drug release profiles showed marked improvement in the drug release rate from the artemether-SEDDS (liquid and powder/solid) as compared to the pure drug. This confirmed that the self-emulsifying formulations release the drug better than the pure drug. The percentage of artemether released from liquid SEDDS, SEDDS powder, marketed formulation and the pure drug in 20 min was 99.1, 45.5, 31.3 and 8.9

%, respectively. The release rate of artemetherSEDDS powder was significantly (P = 0.021) lower than that of the corresponding liquid formulations, similar observations have been reported by other authors.[38, 39] It was explained that hydrophobic drugs exhibit high affinity to the hydrophobic surface of the

silica-based adsorbents. The high afinity will result in preferential diffusion of the hydrophobic drug from the liquid SEDDS to the surface of the adsorbent, forming clusters which will eventually precipitate as a result of its poor solubility in the dissolution medium. The resultant effect of all these events is a lowering of dissolution rates and incomplete recovery of drug in the aqueous phase due to incomplete desorption of the adsorbed liquid formulation from the adsorbent.[38,39] These, therefore, suggest that the potential advantages of solidification of lipid-based formulations by adsorption onto excipients must be balanced carefully against the potential impact on in vivo performance. The release rate of artemether from both liquid and solid SEDDS formulations are however still significantly ($P < 0.005$) higher than those observed in both the pure drug and the marketed formulation. At 30 min, the artemether-SEDDS powder exhibited 1.9 fold increases over the marketed product in the amount of drug released. Significant improvement in dissolution rate indicated improved solubilization of the drug in the aqueous media ostensibly owing to spontaneous emulsification of the lipidic and emulsifying agents to produce the ultrafine emulsions by micellar solubilization.[13]

Pharmacokinetic studies to examine the extent of increase in the bioavailability of artemether from the SEDDS powder in comparison to the pure drug and the marketed formulation could be investigated in rabbits.

CONCLUSION

The solid self-emulsifying formulation was stable and released over 96 % of the drug within 30 min, whereas the marketed product showed barely 50 % drug released. This substantiates the usefulness of the novel drug delivery strategies for overcoming some of the physicochemical challenges associated with the delivery of hydrophobic drug molecules. Artemether-SEDDS can be a viable alternative to the existing artemether formulations and the ease of commercialization associated with solid self-emulsifying formulations suggest that artemether-SEDDS could have a tremendous market potential. The use of the natural oil from sesame seed has the advantage of reliance on cheap, nutritionally acceptable, non-toxic, economically affordable and commercially available raw materials which employs fewer processing steps to provide a stable, compatible and promising alternative.

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