Research Article

Formulation and *in vitro* Characterization of Amorphous Based-Solid Dispersion of An Antimalarial Drug

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ABSTRACT

Solubility is an essential factor for the oral bioavailability of poorly water-soluble drugs. Improving the oral bioavailability of some drugs persist a major problem facing drug formulators. For this, amorphous solid dispersion (S.D) techniques have drawn the interest of many researchers as a means of maintaining supersaturated state and improving the poor aqueous nature of hydrophobic drugs. The present work aimed at improving the oral bioavailability of lumefantrine, a poorly water-soluble antimalarial drug, by using solid dispersion techniques with HPMCAS and Kollidon® 12 PF as carriers to formulate a multi-components solid dispersion. Different generations of the solid dispersion of lumefantrine were prepared using the solvent evaporation method at a different drug: carrier ratio. The formulations were evaluated and characterized using the following parameters: Solubility studies, percentage yield, loading efficiency, micromeritics properties, *in vitro* release studies, Wide angle x-ray diffractions (WXRD) and differential scanning calorimetry (DSC). In the solubility study, Kollidon® 12 PF, Kolliphor® HS 15, HPMCAS, Kolliphor® EL, and aqueous medium had 97, 96, 61, 42 and 11 mg/ml respectively. The formulations exhibited significant flow properties than the physical mixture ($p < 0.05$). Drug release studies showed T_{40} (time to release 40 % of the drug) of 10, 15 and 60 min in PB (pH, 6.8) and 15, 10, and 55 min in SGF (pH, 1.2) from batches H18, H20, and pure drug sample, respectively. The DSC studies indicated the transition of a crystalline form of drug into amorphous formulations, while the WXRD revealed decreased crystallinity. The formulated multi-component solid dispersion of lumefantrine with HPMCAS and Kollidon® 12 PF showed much improvement on the solubility of a poorly aqueous drug.

Keywords: Lumefantrine; Solid dispersion; Kollidon® 12 PF; HPMCAS.

INTRODUCTION

The oral route of drug administration is the most common route of delivery due to convenience and ease of ingestion. Oral route thus confers patient compliance which makes it most common when compared with other routes of administration such as parenteral. The drugs with poor aqueous solubility exhibit dissolution rate limited absorption and hence, show poor bioavailability. This type of drug seems to be a problematic and less effective mode of delivery via the oral route. Various techniques are invoked to improve the solubility challenges such as complexation,[1] self-emulsifying drug delivery system,[2] solid dispersion.[3-5] Solid dispersion has been classified into four generations: first, second, third[6] and fourth.[5, 7] The first generation constituents eutectic mixtures prepared using crystalline carriers like urea and sugars. The second generation solid dispersion involves dispersing drugs molecularly in an irregular form within an amorphous carrier which is usually polymers such as polyethylene glycols, polyvinyl pyrrolidine, polymethacrylates, HPMC, ethylcellulose, Solutol®, etc. The third generation contains mixtures of amorphous polymers and surfactants as carriers. Examples of the substance use as surface active agents or surfactants include Inulin®, compritol, gelucire, Polysorbate 80, Kollidon® HS 15, Kollidon® EL, Kollidon® RH 40, etc. The amorphous drug in solid dispersion is physically more stable than pure form in an amorphous state.[8] The fourth generation solid dispersion has been formulated to contain ethyl cellulose, hydroxypropyl cellulose, Eudragit® RL, Eudragit® RS, poly(ethylene oxide) (PEO) and poly(acrylic acid) (Carbopol®) to obtain controlled release[7] and Kollidon® VA 64.[5] Amorphilization is a technique whereby a solid state form of a drug is transformed from crystalline form to amorphous state. Amorphous solid dispersion is one that contains drug molecularly dispersed in amorphous carriers. Drug stability is being influenced by certain factors such as intermolecular interactions, physical barriers to the crystallization process (local viscosity), antiplasticization effect exerted by the polymer, and the reduction in the chemical potential of the drug.[9] The polymeric carriers equally provide mechanism responsible for improved dissolution rate and absorption, maintaining an *in vivo* supersaturation and precipitation inhibition which is an important factor in improving solubility in the gastrointestinal tract.[10] Reduced particle size leading to an increased surface area is also another factor that could enhance solubility.[11, 12] The miscibility of the drug in the polymer matrix is a necessity for stabilization of solid dispersion product. Therefore, any phase separation can promote API crystallization.[13-15] In addition, a necessary effort is required to formulate miscible solid dispersion systems and protect them from drivers of phase separation such as high temperature, humidity and mechanical stress.[11, 16, 17] The transition from amorphous to crystalline is a thermodynamically driven

phenomenon due to the lower free energy of the crystalline state and is bound to happen at a certain point of time which can occur at a very long time if an external stimulus is not employed. Therefore, external energy needs to be imparted to the system to transit from crystalline to amorphous for example mechanical activation such as milling can generate amorphous forms.[18]

Hydroxypropyl methylcellulose acetate succinate (hypromellose acetate succinate, HPMCAS) is a polymer that contains acetyl and succinoyl groups. Currently, it is used in the novel drug delivery such as solid dispersion.[19-21] There are different types of HPMCAS with different pH of dissolution. Type L, H, and M-HPMCAS dissolve at a pH of ≥ 5.5, ≥ 6.0, and ≥ 6.8 respectively. [22] Research has shown that HPMCAS has been one of the best polymers with crystallization inhibition activity.[19] In contrast, HPMCAS can undergo hydrolysis to produce free acetic acid and succinic acid which may react with drugs due to the locally produced acidic environment.[22]

Kollidon® 12 PF is a vinylpyrrolidone-vinyl acetate copolymer containing the two components in a ratio of 6: 4. A substance containing both hydrophobic and hydrophilic substance improves the surface activity of a poor aqueous drug, controls solubility barriers and then, enhances dissolution and improves absorption and bioavailability of poorly water-soluble drugs. This gives the product its favourable properties as a soluble binder and film-forming agent, particularly for solid dosage forms. It improves solubility, prevents crystal growth on the process of dilution when in contact with a fluid, accelerate disintegration and dissolution rate and give immediate release matrix former of the drug. Lumefantrine is a drug with both permeability and solubility challenges. A drug substance with poor water solubility issue will show dissolution rate limitation and those substances with poor membrane permeability will exhibit permeability rate limited absorption.[23] One of the deficits of the solid dispersion technique is crystallization on storage.

Currently, more efforts are being made to provide supersaturation maintenance ability of formulations *in vivo* thereby inhibiting crystallization. In the polymer selection, maintaining higher concentrations than the thermodynamic solubility after formulation and dissolution both *in vitro* and *in vivo* has been related to higher absorption and therefore, supersaturation maintenance potential of the carrier is an important guiding factor. Some polymer carriers can prevent precipitation by adsorbing onto the surface of nuclei and hinder crystal growth by providing steric stabilization and blocking access to the active surface.[24] HPMCAS and Kollidon® 12 PF have been noted to have such property.[7, 25] In the present work, we attend to achieve good miscibility without aggregation and the much higher degree of supersaturation of lumefantrine, through the formulation of a solid dispersion containing HPMCAS and Kollidon® 12 PF. These multi- components solid dispersion containing HPMCAS and Kollidon® 12 PF play multi-roles by enhancing solubility, amorphous formation, crystallization inhibition, and bioavailability of lumefantrine. Therefore, there will be an improvement in the poor aqueous solubility and permeability of lumefantrine as the incorporated agents HPMCAS and Kollidon® 12 PF will synergistically enhance solubilization and prevent crystal formation of the product on storage and eventually, prevent potential *in vivo* crystallization that may occur due to supersaturation.

MATERIALS AND METHODS

Materials

Hydroxypropyl methylcellulose acetate succinate (Shin-Etsu, Chem company, Japan), Lumefantrine (CAS71963-77-4 Hangzhou Dayangchem co., limited, free gift), Kollidon® 12 PF (free gift from BASF). All other reagents and solvents used were of analytical grade.

Methods

Solubility Studies

Different polymers, carriers, and solvents were screened for solubilization of lumefantrine by saturation solubility method. The solubility of the lumefantrine in each of the carriers and the excipients was determined by dissolving the excess amount of lumefantrine in 3 ml of each of the selected carrier solution in a test tube. The test tubes were shaken at time intervals with a mechanical shaker for 24 h under an ambient condition of temperature. The supernatants were taken and analyzed for lumefantrine content using UV/Vis. Spectrophotometer (Spectrumlab 752, Netherlands) and the vehicle with high solubility profile was used for further studies.

Preparation of Lumefantrine-Loaded Solid Dispersion using solvent evaporation method and physical mixture

A lumefantrine-loaded solid dispersion was prepared with HPMCAS as a carrier in various ratios using solvent evaporation method to obtained batches H1 – H18.[5] The physical mixture was prepared by mixing the components together without solvent and was obtained as PM19 – PM21. The amount of lumefantrine loaded was constant in all the batches prepared with the varied ratio of carriers as shown in Table 1.

Determination of Percentage Yield

Each of the formulation was accurately weighed. When dried, the weights were recorded as the yield (W_1). The theoretical weight (W_2) of each of the formulation was obtained. The percentage yield was calculated as:

$$\text{Percentage yield (\%)} = \frac{W_1}{W2} \text{ X } \frac{100}{1} \quad \text{..... Eqn 1}$$

Determination of Loading Efficiency

An equivalent of 80 mg of lumefantrine was weighed out from each of the ratios and placed in a beaker containing 10 ml of methanolic HCl and stirred to dissolve the solid dispersion and filtered. The volume was then made up to 100 ml with methanolic HCl. The resulting solution was

analyzed by using a UV spectrophotometer (Spectrumlab 752, Netherlands) at 335 nm wavelength. The methanolic HCl was used as a blank. The loading efficiency (%) was determined as in equation 2.

$$\text{Loading efficiency} = \frac{Actual\ loaded\ Concentration}{Theoretical\ drug\ loaded} \times \frac{100}{1} \quad \text{...Eqn 2}$$

Table 1: Formula ratios for HPMCAS-lumefantrine SDs.

Batch	Lumefantrine	HPMCAS	Kolliphor® EL	Kolliphor HS 15®	Kollidon® PF 12
H1	1	1			
H2	1	2			
H3	1	3			
H4	1	1	0.5		
H5	1	2	0.5		
H6	1	3	0.5		
H7	1	1	0.5		1
H8	1	2	0.5		1
H9	1	3	0.5		1
H10	1	1		0.5	
H11	1	2		0.5	
H12	1	3		0.5	
H13	1	1		0.5	1
H14	1	2		0.5	1
H15	1	3		0.5	1
H16	1	1	0.5	0.5	1
H17	1	2	0.5	0.5	1
H18	1	3	0.5	0.5	1
PM19	1	1	0.5	0.5	1
PM20	1	2	0.5	0.5	1
PM21	1	3	0.5	0.5	1

H1-3: 2nd generation; H4-H6 and H10-H12: 3rd generation; H7-H9. H13-H15 and H16-H18: 4th generation of solid dispersion by solvent evaporation technique; PM19-PM21 represent physical mixtures; SDs: solid dispersions.

Flow Properties

Bulk and Tapped Density

A 1.5 g of each of the samples was weighed out and placed in a 10 ml graduated cylinder. The volume occupied by the powder was noted and recorded as the bulk volume in triplicate. The bulk density was obtained from equation 3.

$$\text{Bulk density} = \frac{Mass\ of\ powder\ (g)}{Bulk\ volume\ of\ powder\ (Ml)} \quad \text{..... Eqn 3}$$

The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one inch at 2 seconds interval until there was no change in volume. This volume was taken as the tapped volume. The tapped density was calculated as shown in equation 4.

$$\text{Tapped density} = \frac{Mass\ of\ Powder\ (m)}{tapped\ volume\ of\ powder\ (VT)} \quad \text{..... Eqn 4}$$

Flow Rate and Angle of Repose

A funnel was properly clamped at 7.5 cm from a flat surface on the retort stand. The various samples with known weight were gradually placed into the funnel with the orifice of the funnel closed. Upon opening the orifice, the time it took for all the powder samples in the funnel to flow out through the orifice was noted and flow rate calculated using equation 5, while the height and radius of the powder heap were determined using a meter rule and angle of repose was determined from equation 6.

$$\text{The flow rate of powder (g/s)} = \frac{mass\ of\ powder\ (g)}{time\ of\ flow\ (s)} \quad \text{..... Eqn 5}$$

$$\text{The angle of repose } (\theta) = \tan^{-1}\left(\frac{height\ of\ powder}{radius\ of\ the\ heap\ of\ powder}\right) \quad \text{.... Eqn 6}$$

Compressibility Index and Hausner's Quotient.

Compressibility Index and Hausner's quotient were calculated from equation 7 and 8.

$$\text{Carr's Index (\%)} = \frac{Tapped\ Density - Bulk\ density}{tapped\ desnsity} \quad \text{..... Eqn 7}$$

$$Hausner's\ quotient = \frac{Tapped\ density}{Bulk\ density} \quad \text{..... Eqn 8}$$

***In vitro* drug release Study**

The dissolution rate of the drug from different formulations of solid dispersion was studied in phosphate buffer (pH, 6.8) and simulated gastric fluid (SGF, pH, 1.2). The dissolution apparatus (magnetic stirrer) set at 50 rpm was used to generate drug release profiles. A known quantity of lumefantrine solid dispersion (equivalent of 80 mg) was filled into a hard gelatin capsule and lowered into the dissolution medium that was maintained at 37 ± 0.5 ° C. After 5, 10, 15, 20, 25, 30, 35 and 60 min, 5ml aliquots of the release medium was withdrawn and diluted to 20 ml (4 fold dilutions) and assayed at absorbance maxima 335 nm

using UV spectrophotometer. At every interval, 5 ml of the fresh medium set at same condition was added to replace the withdrawn sample. This was done for all the samples in triplicates.

Characterization of lumefantrine-HPMCAs based-Solid Dispersion

Differential Scanning Calorimetry (DSC)

Melting transitions and changes in heat capacity of lumefantrine, lumefantrine-loaded solid dispersion and the excipients were determined using a differential scanning calorimetry (Netzsch DSC 204 F1, Geratebau, GmbH, Selb, Germany). About 1.00 mg of each sample was weighed into an aluminum pan, hermetically sealed and the thermal behaviour determined with range 20-500 ^{o} C, at a heating rate of 10 K/min under a 20 ml/min nitrogen flux. The thermal properties such as the melting transitions and enthalpies were noted.

Wide angle x-ray diffraction (WXRD)

The change in gallery height of the blend was investigated by WAXD experiments, which was carried out using an X-ray diffractometer (BEDE D-3 system) with Cu Kα radiation at a generator voltage of 40 kV and a generator current of 100 mA. Samples were scanned from 2θ = 1-100^{o} at a scanning rate of 2 ^{o}/min.

Statistical analysis

The statistical analysis of loading efficiency and flow properties of the batches in this research work were carried out using GraphPad InStat Demo (USA). Values were expressed as mean ± SD (standard deviation). Data were calculated and analyzed with one way analysis of variance (ANOVA). Differences between means were assessed by a two-tailed student's T-test and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Solubility Studies

Solubility studies were carried out to identify the excipients having a maximal solubilizing potential for the drug. This helped to achieve optimal drug loading. From the result as presented in Fig. 1, had 97, 96, 61, 42 and 11 mg/ml were obtained for Kollidon® 12 PF, Kolliphor® HS 15, HPMCAS, Kolliphor® EL and aqueous medium respectively. Lumefantrine showed the highest solubility in Kollidon® 12 PF followed by Kolliphor® HS 15.

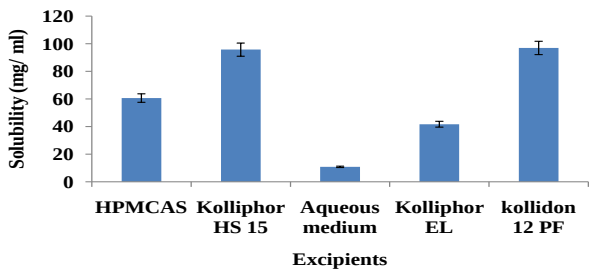

Figure 1: Solubility study of lumefantrine in different carriers.

Loading Efficiency (LE %) and Percentage yields

The result of loading efficiency (LE %) and percentage yields are presented in Table 2. The obtained LE were in the range of 60 ± 0.49 – 63 ± 0.41, 74.8 ± 0.40 – 75 ± 0.89, 88.6 ± 0.50 – 95.9 ± 0.46, 51.2 ± 0.29 – 77.7 ± 0.31, 55.2 ± 0.31 – 91.6 ± 0.84, 72.8 ± 0.32 – 97.6 ± 0.36 and 20.9 ± 0.24 – 76.6 ± 32 % for batches H 1 - H3 (2nd gen), H4 - H6 (3rd gen), H7 - H9 (4th gen), H10 - H12 (3rd gen), H13 - H15 (4th gen), H16 - H18 (4th gen) and PM19 - PM21 (physical mixture). The fourth generation (4th gen) solid dispersion formulations had significantly higher loading efficiency ($p < 0.05$) followed by third generation (S.D) and lastly the physical mixture. This showed that lumefantrine really had high solubility in the batches containing Kollidon® 12 PF (4th gen) S.D. Even though the physical mixture also contained Kollidon® 12 PF but because the drug is not molecularly dispersed just like in the S.D batches, it showed low encapsulation efficiency. Equally the 4th gen batches gave the highest percentage yield as shown in Table 2.

Table 2: Loading efficiency and percentage yields of the formulations

Batches	L. E (%) ± Sd	Percentage yield (%)
H1	60. 4 ± 0.49	78.0
H2	60. 4 ± 0.39	74.6
H3	63.2 ± 0.41	71.0
H4	75.0 ± 0.89	59.2
H5	75.0 ± 0.90	70.5
H6	74.8 ± 0.40	77.6
H7	88.7 ± 0.60	80.4
H8	95.9 ± 0.46	71.1
H9	88.6 ± 0.50	88.1
H10	65.8 ± 0.34	66.2
H11	51.2 ± 0.29	79.1
H12	77.5 ± 0.39	76.7
H13	90.3 ± 0.39	93.4
H14	91.6 ± 0.84	87.9
H15	55.2 ± 0.31	89.3
H16	72.8 ± 0.32	78.6
H17	85.2 ± 0.50	92.2
H18	97.6 ± 0.36	81.2
PM19	20.9 ± 0.24	79.4
PM20	76.6 ± 0.32	95.9
PM21	42.3 ± 0.64	89.9

H1-18: Lumefantrine-HPMCAS solid dispersion by solvent evaporation technique; PM19-PM21: physical mixtures; L.E: loading efficiency; Sd: standard deviation.

Flow properties

The result of the flow properties of the SD batches is presented in Table 3. The various batches of the solid dispersion formulations had fair flow properties based on the angle of repose. This might be due to molecular aggregation of particles. Though considering Carr's index, values in the range of 5-15 indicate excellent flow, 16-18 good flow, 22-35 poor flow, 36-40 very poor flow and above 40 extremely poor flow. Most of the batches had their Carr's index within excellent and good flow range. The solid dispersion formulations have their Hausner's ratio to be less than 1.25 which indicated good flow property. The values for the physical mixtures were all above 1.25 indicating their poor flow. The flow rate values for the solid dispersion were greater than that of the physical mixtures, implying that the formulations have a significant ($p < 0.05$) flow property than the physical mixture.

Table 3: Flow Properties of the SDs

Batch	BD (g/ml ± Sd)	TD (g/ml ± Sd)	CI (%)	HQ	AOR (° ± Sd)	FR (g/s ± Sd)
H1	0.429 ±1.20	0.536±0.87	20.0	1.25	42 ±1.05	1.5±2.48
H2	0.469 ±1.42	0.517 ±0.85	9.00	1.10	52±0.95	1.9±0.95
H3	0.441 ±0.87	0.500±0.76	11.8	1.13	54 ±0.88	2.9±2.10
H4	0.429 ±0.94	0.536±0.95	20.0	1.25	45 ±0.94	0.7±2.95
H5	0.417±0.44	0.500 ±0.44	16.6	1.20	48±0.37	1.0±0.90
H6	0.441±0.28	0.517±0.57	14.7	1.17	48±0.49	3.1 ±1.24
H7	0.429±0.94	0.536±0.54	20.0	1.25	50±2.41	1.2±3.40
H8	0.441±0.86	0.517±0.09	14.7	1.17	54±1.87	2.4±2.45
H9	0.429±0.49	0.536±0.37	20.0	1.25	50 ±2.08	1.2±2.85
H10	0.417 ±0.71	0.500±0.87	16.6	1.20	54±2.17	0.6±3.15
H11	0.441 ±1.24	0.536±0.47	17.7	1.22	50±2.08	0.8±5.45
H12	0.455±2.42	0.600±0.56	24.2	1.23	56±1.12	1.0±0.95
H13	0.441±0.95	0.536 ±0.25	17.7	1.22	42±0.87	3.3±0.57
H14	0.429±0.34	0.517±0.49	18.8	1.21	54 ±1.44	3.2±1.15
H15	0.429±0.94	0.536±0.53	20.0	1.25	27 ±1.24	2.0±0.98
H16	0.417 ±1.30	0.484±0.59	13.8	1.16	48±2.28	4.5±0.98
H17	0.441±1.42	0.500±1.25	17.8	1.13	52±0.94	2.8±0.98
H18	0.441 ±0.23	0.536 ±0.97	17.7	1.22	35±2.14	2.3±2.15
PM19	0.429 ±0.87	0.557±1.36	23.0	1.29	50±2.06	0.7±0.59
PM20	0.455 ±0.35	0.589±1.44	22.8	1.29	52±0.95	0.8±2.46
PM21	0.484 ±0.95	0.633±0.87	23.5	1.30	58 ±2.18	1.0 ±3.57

H1-18: solid dispersions, PM19-21: physical mixtures; BD: Bulk Density; TD: Tapped Density; HQ: Hausner's Quotient; CI: Carr's Compressibility Index; FR: Flow Rate; AOR: Angle of Repose; Sd: standard deviation.

***In vitro* Release Studies**

An *in vitro* release of lumefantrine from SDs was evaluated in both simulated gastric fluid (SGF), pH, 1.2 and phosphate buffer (PB), pH, 6.8 and the results presented in Figs. 2 and 3. Batch H18 from the fourth generation was selected for this study based on its highest loading efficiency among the SD batches and PM20 was from the physical mixture batch and they were compared with the pure drug sample. The results showed T_{40} (time to release 40 %) of 10, 15 and 60 min in PB (pH, 6.8) and 15, 10, and 55 min in SGF (pH, 1.2) from formulations H18, PM20, and pure drug sample, respectively. Initially, there was a slow release of the drug of batch H18 in both media which might be due to the gelatinous layer of HPMCAS formed around the molecularly dispersed drug upon contact with an aqueous medium which might be acting as a drug release barrier unlike in PM20 and pure drug sample. As the time of release increased (≥ 15 min), the release pattern changed in favour of batch H18. Batch H18 which was formulated with Kollidon® 12 PF, HPMCAS and double surfactant (1:1) ratio significantly ($p < 0.05$) had the highest drug release > 80 %. Lumefantrine solid dispersion had higher percentage release in the simulated gastric fluid (pH, 1.2) than in the phosphate buffer (pH, 6.8). This is due to the fact that lumefantrine as a basic drug which was molecularly dispersed in the carriers will easily ionized and go into solution in acidic medium SGF (pH, 1.2) than in phosphate buffer, PH 6.8. The pure sample of lumefantrine exhibited almost the same release pattern with the physical mixture. It has been reported that nucleation is an important step that determines the supersaturated concentration of a drug.[26] HPMCAS is one of the nucleation inhibitors for amorphous molecules. The binary polymeric activity of HPMCAS and Kollidon® 12 PF exhibited higher supersaturation stability and solubility for lumefantrine. This could be observed from the release profile, where the drug release of batch H18 was higher and faster than pure drug sample and the physical mixture. This improvement of

the drug release can also be related to other factors such as the enhancement of wetting and solubilization by a hydrophilic carrier and the reduction of the drug particle size as well as reduced particle aggregation as the drug is molecularly dispersed in the carriers. On the contrary, the physical mixture and pure drug samples which were in powder forms can agglomerate in the medium and their effective surface areas were smaller than the actual surface area. This might lead to a decrease in drug release. Equally, many times powders float on top of the medium due to poor wettability which also can cause less exposure to the dissolution medium. Broadly speaking, an amorphous form of a drug is thermodynamically unstable and has a tendency to revert to the equilibrium state via recrystallization of a drug. Therefore, precipitation inhibitors such as HPMCAS are known to inhibit the recrystallization of drugs and thus maintain the supersaturation of the drug in the dissolution medium.

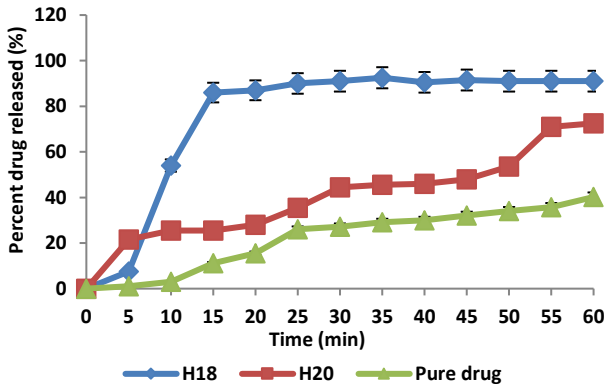

Figure 2: A release profile of lumefantrine SD in phosphate buffer (pH, 6.8).

H18 as 4th generation and multicomponent solid dispersion; H20 as physical mixture

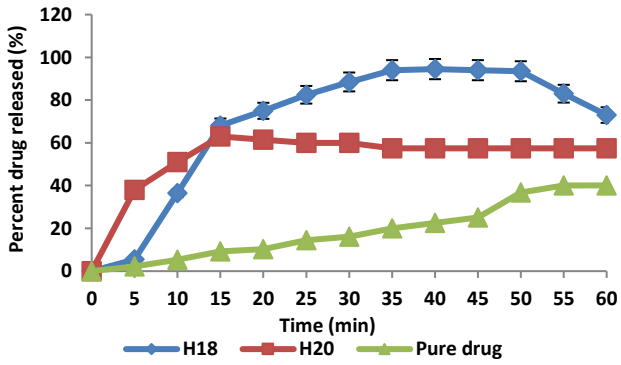

Figure 3: The release profile of lumefantrine SD in SGF (pH, 1.2)

H18 as 4th generation and multicomponent solid dispersion; H20 as physical mixture

Differential Scanning Calorimetry

The method of differential scanning calorimetry (DSC) allows measurement of the energy flow to and from a sample during a temperature-controlled experiment. DSC is one of the most widely used techniques to study solid state, and especially to determine compound purity, stability, and polymorphism.[27] DSC technique relies on the principle that solid-state modifications are characterized by different melting points and melting enthalpies.[28] DSC was carried out in order to study thermotropic properties of lumefantrine and other excipients used in the formulation as presented in Fig. 4. The results of the thermal properties of the lumefantrine, Kolliphor® HS 15, Kolliphor EL®, Kolliphor® 12 PF, batch B18. The DSC thermograms of HPMCAS showed a broad endothermic peak at 360.9 ° C. This broadness implied that it has an amorphous nature which molecularly entrapped the drug. This will create more pores for the drug localization which will enhance drug release, loading efficiency of the drug.[5, 29, 30] Therefore, HPMCAS will be capable of exhibiting good role as a drug carrier. The DSC curves of Kolliphor® HS 15 and Kolliphor® EL also showed broad endothermic peaks at 65 ° C and 58.8 ° C, respectively. They exhibited broader peaks implying that they have amorphous nature which at their molecular state will uniformly disperse the drug to enhance the solubility in an aqueous medium and therefore, played good roles of solubilizers. Kollidon® 12 PF had a less crystalline endothermic melting peak at 65 ° C. The DSC thermograms of batch H18 SD containing lumefantrine, HPMCAS, Kolliphor® HS 15, Kolliphor® EL, and Kollidon® 12 PF formulation showed broader and decrease in endothermic peak of lumefantrine at 126 ° C. The reduction in the enthalpy and height of the drug could mean that the drug is transforming to amorphous state which means creation of more pores for the drug localization. Thereby enhancing the drug release and loading efficiency. From the curves, it could be inferred that the solvent evaporation method used had no negative effect on the formulation rather it had an improvement as the melting peak of lumefantrine in the formulation was closer to that of pure lumefantrine indicating purity state.

Wide angle x –ray diffraction (WXRD)

The WAXRD of lumefantrine, batches H5, H8, H18, and H20 are presented in Fig. 5, while the interposed diffractograms of (a) H11 and H18 (b) H5 (3rd gen) and H17 (4th gen). The peaks of lumefantrine showed a crystalline state of the drug. The formulations have almost the same peak intensity showing that they have the same stability. The peaks of the formulations indicated a decrease in the crystalline intensity meaning there is a reduction of the crystalline state of the drug leading to an increase in the amorphicity of the SDs. This amorphous nature of the formulations generated more pores within the matrix for drug entrapment which improved solubility, drug releases, and absorption. Also, the interposed diffractograms (Fig. 6) indicated more decrease in the crystalline intensity of the fourth generation SDs (H17 and H18) than third-generation SDs (H5 and H11).

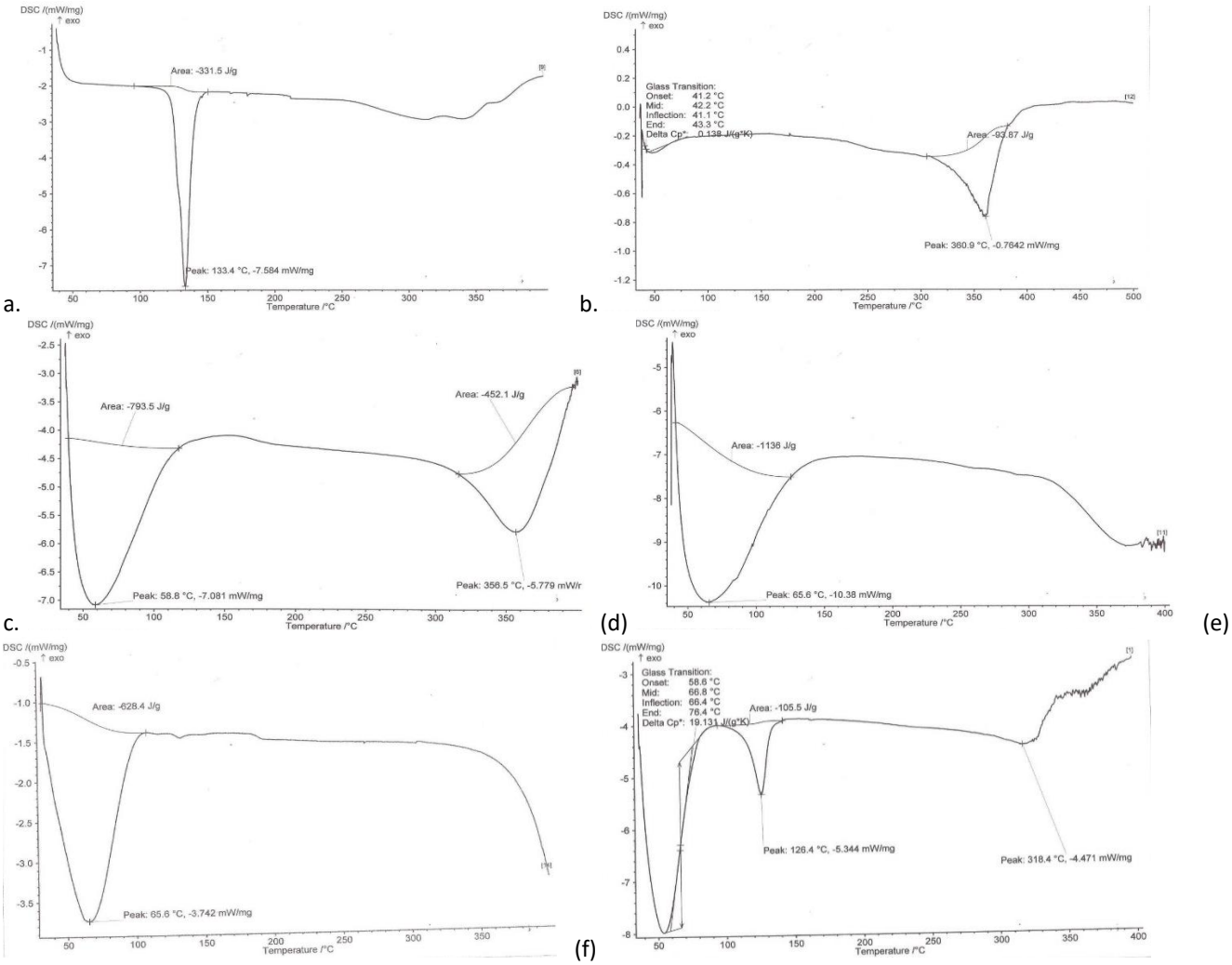

Figure 4: The DSC thermograms of (a) lumefantrine (b) HPMC (c) Kolliphor® EL (d) Kolliphor® HS 15 (e) Kollidon® 12 PF (f) Batch formulation H18.

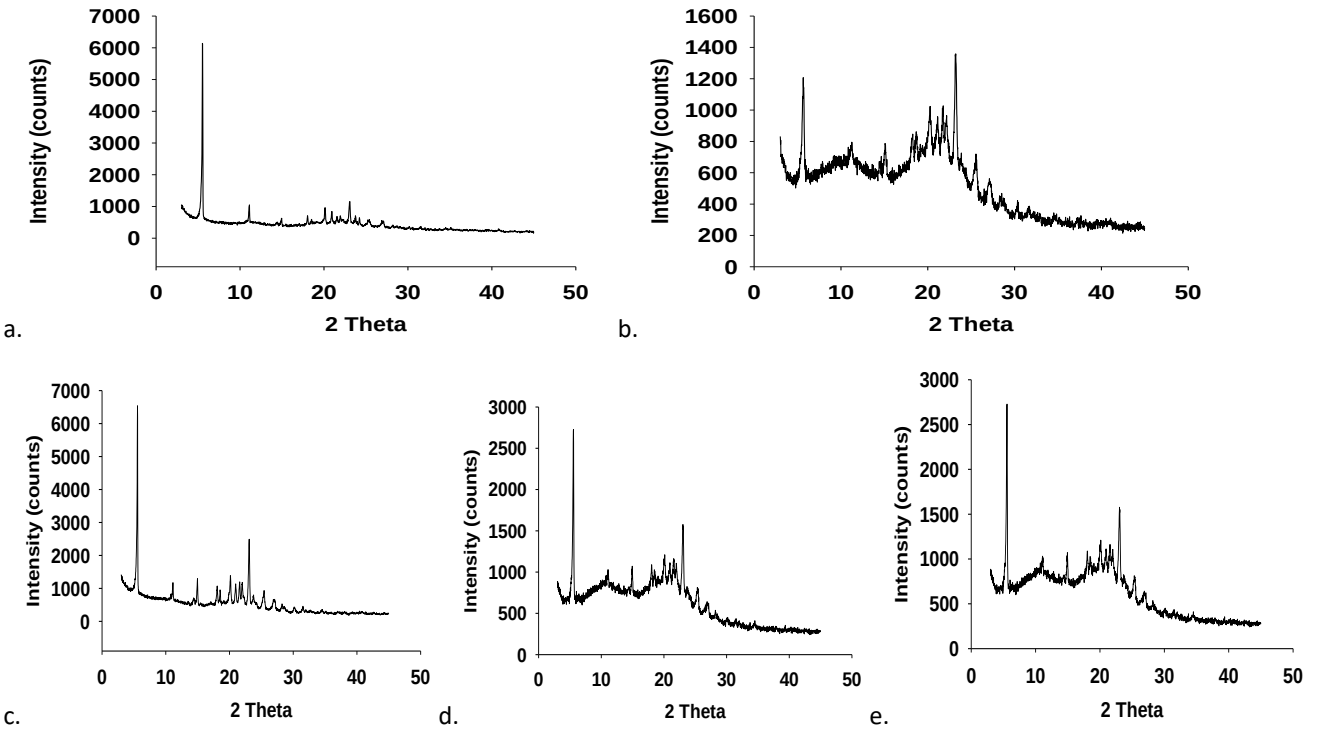

Figure 5: Thermograms of (a) lumefantrine (b) H18 (c) H5 (d) H8 (e) H20
H5, H8 and H18: 2nd, 3rd and 4th (multicomponent) generation of solid dispersion by solvent evaporation technique.

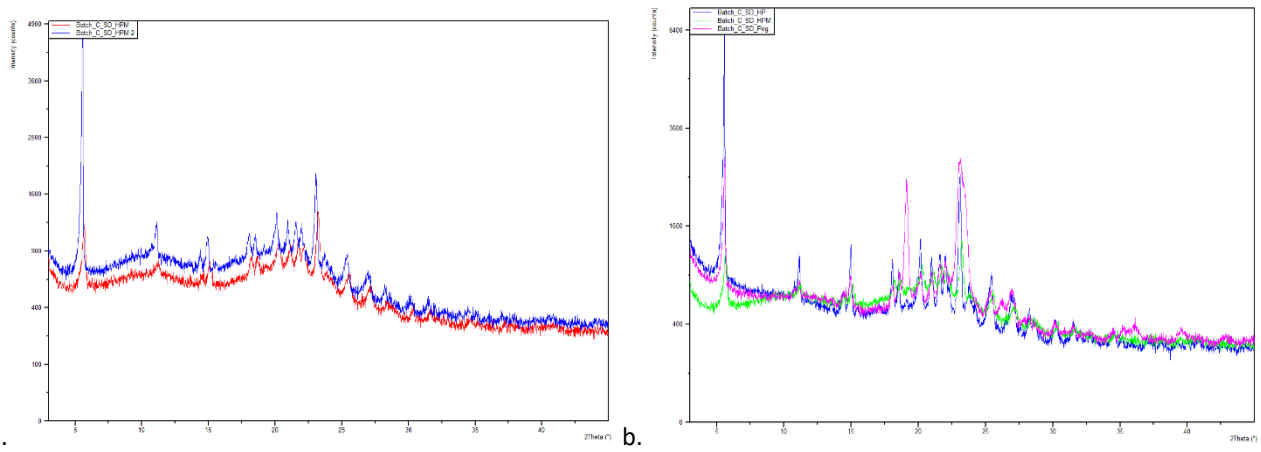

Figure 6: Diffractograms of solid dispersions: (a) H11 (3rd gen) and H18 (4th gen and multicomponent), and (b) H5 (3rd gen) and H17 (4th gen)

CONCLUSION

The solid dispersion technique is a good technique for the formulation of poorly water-soluble drug such as lumefantrine by reducing particle sizes, the formation of amorphous forms and improved wettability. From the flow properties evaluated, the angle of repose of the SD formulations was observed to have improved flow behaviours due to agglomerate of the particles that are already in the molecular state. The fourth generation of solid dispersion significantly showed higher loading efficiency and drug release than other generations. DSC of the formulations showed broader peaks which indicated amorphous existence of lumefantrine, while the WXRD indicated less crystallinity of the drug in the carriers with the formulations interposing well-meaning that there was no interaction of excipients. Therefore, a combination of HPMCAS and Kollidon® 12 PF gave a synergistic stabilization of the lumefantrine molecules in the SD formulations. It could be deduced that the solid dispersion formulations especially the fourth generations achieved amorphous formulations which enhanced more pores for localization of drugs, thereby enhancing the release of the drug.

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