

# Solid Dispersion of Lumefantrine Using Soluplus® by Solvent Evaporation Method: Formulation, Characterization and *in-vitro* Antimalarial Screening

Pranita Sunil Kanojiya\*, Yogita Charde, Jasmine Gev Avari, Rita Naresh Wadetwar

Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Amravati Road, Nagpur, Maharashtra, INDIA.

## ABSTRACT

**Objectives:** Lumefantrine (LUM) is an antimalarial drug having poor aqueous solubility. The objective was to formulate the solid dispersion of LUM and improve the solubility and dissolution rate. **Materials and Methods:** Solvent evaporation technique was used to prepare solid dispersions (SDs) with Soluplus® (SOL) using a rotary evaporator. The feasibility of the formation of SD for LUM and SOL was assessed by the Hansen solubility parameter. The drug solubility was analyzed by the HPLC method and the ratio of LUM: SOL was optimized to 1:2. The SD was characterized by DSC, FTIR, XRD and SEM. **Results:** The results showed that the LUM and SOL had groups that lead to the interaction between them and this led to conversion from crystalline to amorphous form and thus improved the dissolution rate. The solubility of L2 was found to be  $135 \pm 3.3 \mu\text{g/mL}$  using the selected dissolution media (0.1 N HCl + 1% Myrj 52). The *in-vitro* antimalarial screening was performed using the *P. falciparum* 3D7 strain and the *in-vitro* cytotoxicity test was performed using the Vero cell line. The higher antimalarial efficacy of L2 SD was observed as compared to plain LUM. The selectivity index value of LUM SD depicted its non-toxicity. Stability study was carried out for three months and the SDs were evaluated for the drug content, change in weight and *in-vitro* drug release. No significant changes were observed after three months in the drug content, SD weight and *in-vitro* drug release. Thus the L2 SD was found to be stable. **Conclusion:** The prepared SD improved the solubility as well as the dissolution rate of the drug.

**Key words:** Lumefantrine, Soluplus, Solubility enhancement, Dissolution rate, Antimalarial screening.

**Key message:** The prepared solid dispersion improved the solubility and dissolution rate of Lumefantrine by using the hydrophilic polymer. The hydrophilic matrix aided in the solubilization of the drug into the aqueous environment and thus proved to be efficacious.

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**Correspondence:**

Miss. Pranita Sunil Kanojiya

Research Scholar,  
Department of Pharmaceutical  
Sciences, Rashtrasant Tukadoji  
Maharaj, Nagpur University,  
Amravati Road, Nagpur-440  
033, Maharashtra, INDIA.

Email id: kanojiyapraniti06@gmail.com

## INTRODUCTION

Malaria is the most prevalent parasitic disease caused by Apicomplex protozoan of the *Plasmodium* (P.) genus.<sup>1</sup> It is one of the most serious vector-borne diseases affecting millions of people who reside exclusively in the hotter and moist areas of the tropics.<sup>2</sup> Five different species of Plasmodium known to cause malaria in human beings are *P. vivax*, *P. falciparum*, *P. malariae*, *P. ovale* and *P. knowlesi*.<sup>3</sup>

Lumefantrine is a widely used antimalarial drug in malaria-endemic areas.<sup>4</sup> Many

studies have demonstrated that it is highly effective in the treatment of resistant *P. falciparum* malaria, resulting in high cure rates and prevention against reinfection.<sup>5</sup> It is having poor solubility and poor permeability, belonging to BCS class IV drug and employed for the treatment of severe multi-resistant malaria and is present in the essential medicine list of WHO. It is active against *P. vivax*, *P. falciparum* strains of chloroquine-sensitive and chloroquine-resistant and also used for management



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of cerebral malaria. However, the therapeutic effect is inconsistent due to the poor oral bioavailability resulting in delayed action of the drug.<sup>6</sup>

Several approaches have been adopted to improve the dissolution and/or solubility of drugs by the use of prodrugs, complexation methods with cyclodextrin, micronization and crystal technology, nanotechnology, etc. However, these approaches have their limitations such as failure to form active forms *in vivo*, laborious methods of preparation, the formation of agglomerates and toxicity issues.<sup>7</sup>

Solid dispersions (SDs) are efficient in improving the oral bioavailability by forming a highly soluble and stable amorphous form of drugs. In the SD system, the hydrophobic drug is dispersed at a molecular level in hydrophilic carrier which increases solubility of the drug and as a result of the formation of a stable drug-carrier matrix system, there is prevention of crystallization tendency of the drug from amorphous to crystalline form. As the drug exists in the molecular or amorphous or microcrystalline state, the solubility and wettability of drugs are improved which increases the dissolution rate of the drug. Solvent evaporation is a widely used method for preparing solid dispersions at a micro scale and includes the solubilization of drug and carrier in a volatile solvent and the advantage of this method is that thermal degradation of drug or polymers are inhibited since the process can be carried out at low heating temperatures.<sup>8,9</sup>

SDs have influence on the drug parameters such as crystallinity and solubility. Solid dispersion consists of one or more therapeutic agents in an inert polymer matrix. Solubility enhancement by polymer takes place by mechanisms such as micellar solubilization, reducing interfacial tension, imparting hydrophilicity, supersaturation of the drug in the solution. The main criteria for such polymers include biodegradability, biocompatibility and must have hydrophilic groups. These polymers improve the solubility of the drug in water and thus enhance the bioavailability of the drug in the body. Mostly the polymers used for solid dispersions lead to amorphization of the crystalline drug and also reduce the particle size. Thus, the energy required for overcoming the barrier of crystal lattice reduces because of the amorphous nature of the drug.<sup>10</sup> Examples of hydrophilic carriers are Poloxamer 407, polyvinylpyrrolidone PVP K30, PVP VA64, Gelucire 50/13 and PEG 6000.<sup>11-14</sup> These polymers are generally recognized as safe with favorable properties to prepare SDs. The SD has emerged as a guiding tool for poorly soluble drugs that increases the bioavailability and gears up the dissolution rate-limited process, improving the

efficacy of drug by modulation of the drug permeability through active membranes and reduction of adverse effects.<sup>15</sup> Then, SD can be employed to produce solid and liquid pharmaceutical form such as suspension, tablets and capsules.<sup>16</sup>

Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) is a polymer having amphiphilic nature and used as a carrier matrix and solubilizer. It plays the role of both carrier and active solubilizer (through micelle formation in water) and can be considered as the fourth generation carrier of solid dispersions.<sup>17,18</sup> Preparation of SDs using solvent evaporation has been successfully explored for the dissolution rate enhancement of poorly water-soluble drugs.<sup>19,20</sup>

In the present study, an attempt was made to increase the aqueous solubility of LUM by solid dispersion (Solvent evaporation) technique using Soluplus as the hydrophilic polymer.

## MATERIALS AND METHODS

LUM was generously gifted by Mangalam Drugs and Organics Ltd., (Mumbai), India. Soluplus was supplied by BASF Corporation, Mumbai, India (Head office Ludwigshafen, Germany). The solvents used for the HPLC system were of HPLC grade. All other chemicals used were of analytical grade.

### HPLC method

A Shimadzu Prominence liquid chromatography model LC20AD equipped with DGU-20A5 degasser along with SPD-M20A PDA detector was used with LC solution software. The analytical column used was Princeton Chromatography INC C<sub>-18</sub> (250mm×4.6mm) with a particle size of 5 µm. The buffer was prepared using 5 mL of triethylamine in 1000 mL of water and then pH was adjusted to 3.0 ±0.05 with the help of orthophosphoric acid using a digital pH meter (Digital pH-meter, Elico Pvt. Ltd., India). The mobile phase was prepared by mixing buffer and acetonitrile (20:80, v/v) that was settled to flow with a flow rate of 1.0 mL/min. The volume of the sample used was 20 µL for injection and the wavelength of detection was adjusted to 210 nm. The stock solution of LUM was prepared by dissolving 240 mg of LUM in 25 mL of mobile phase previously added into a 100 mL volumetric flask and then 1 drop of orthophosphoric acid was added. Then the solution was dissolved properly, sonicated and was made up to 100 mL with the mobile phase. The standard solution was prepared by taking a 5 mL solution from the LUM stock solution and diluting it with the dissolution medium

up to 100 mL to have a concentration of 120 µg/mL. The resulting solution was filtered through a nylon filter paper having a pore size of 0.45 µm.<sup>21</sup> A calibration curve was plotted as the area under curve vs. concentration of LUM (over a range of 120-600 µg/mL) and the linear regression equation ( $y = mx + b$ ) was obtained.

### Determination of solubility parameter

The solubility parameter is used as an indicator of the drug and polymer miscibility along with physical stability. It serves to be a screening tool for the selection of polymers for preparing solid dispersion. Many studies have utilized the solubility parameter for the same. The group contribution method was applied due to its feasibility for the determination of the solubility parameter. By using the Hoftyzer and Van Krevelen method, the Hansen solubility parameters of the drug and the polymers were calculated. For polymers, the determination of the solubility parameter was based on the average molecular weight.<sup>20,22-25</sup>

### Preparation of solid dispersion

The solvent evaporation method was adopted for preparing solid dispersions. The carrier (SOL) and the drug was accurately weighed using a digital weighing balance (Electronic balance, AUX 120, Shimadzu, Japan), this physical mixture was solubilized in a minimum amount of common solvent i.e. chloroform in a 250 mL round bottom flask (RBF) till the mixture dissolved completely. Then the solvent was evaporated using a rotary vacuum flash evaporator equipped with a water bath having a digital temperature controller (Jain scientific glassworks, India.) fitted with RBF was kept at temperature 60°C until the wet mass was obtained. The residue was collected and then kept for drying in a hot air oven (Spectra Equipments, Hyderabad) at 37°C until the constant weight was achieved. This solid residue was pulverized using a porcelain mortar and pestle. The pulverized powder was passed through sieve No.50 and stored in desiccators for further studies.<sup>26,27</sup>

### Gibbs free energy $\Delta G^\circ_{tr}$

The Gibbs free energy  $\Delta G^\circ_{tr}$  value indicates whether the drug and hydrophilic polymer gets miscible or not and the spontaneity of the reaction and was calculated using the following equation:

$$\Delta G^\circ_{tr} = \{-2.303RT \log\left(\frac{S_0}{S_s}\right)\}, \quad (1)$$

Where  $S_0/S_s$  is the ratio of the molar solubility of LUM before treatment and after treatment with SOL, R is the general gas constant (8.314 J K<sup>-1</sup>mol<sup>-1</sup>) and T is

the absolute temperature in Kelvin. Negative Gibbs-free energy values indicate improved dissolution.<sup>28,29</sup>

### Flory-Huggins interaction parameter ( $\chi$ )

Miscibility of the drug with the polymer can also be studied by monitoring the changes of the onset temperature in the melt endothermic peak and heat of fusion ( $\Delta H_f$ ) of the drug. For miscible drug-polymer systems, lowering of the drug melting point due to the presence of polymer is well documented<sup>27,28</sup> and can be related to the Flory-Huggins interaction parameter ( $\chi$ ) which was evaluated from melting point depression data obtained from the DSC plot, using the following equation:

$$\frac{1}{T_{m,mix}} - \frac{1}{T_{m,pure}} = -\frac{R}{\Delta H_f} \left( \ln \phi_{drug} + \left(1 - \frac{1}{m}\right) \phi_{polymer} + \chi \phi_{polymer}^2 \right), \quad (2)$$

where  $T_{m,mix}$  is the melting temperature of the LUM in the presence of the polymer,  $T_{m,pure}$  is the melting temperature of the LUM in the absence of the polymer,  $\Delta H_f$  is the heat of fusion of the pure LUM,  $m$  is the ratio of the volume of the polymer to that of LUM and  $\phi_{drug}$  and  $\phi_{polymer}$  are the volume fractions of the LUM and the polymer respectively.<sup>28,29</sup>

### Solubility studies for the selection of dissolution media

An excess quantity of the drug was placed in 20 mL capacity vials containing 10 mL of dissolution media separately for each type of dissolution medias. The dissolution medias used for study were distilled water, 0.1 N HCl pH 1.2, phosphate buffer pH 7.2, distilled water +1% Myrj 52, distilled water +1% SLS, 0.1 HCl buffer pH 1.2 +1% Myrj 52, HCl buffer pH 1.2 +1% SLS, phosphate buffer pH 7.2 +1% Myrj and phosphate buffer pH 7.2 +1% SLS. The samples were sonicated (Ultrasonicator, PCi, Mumbai, India) for 20 min at room temperature and capped vials were shaken for 48 hrs at  $37 \pm 0.1^\circ\text{C}$  with the speed 75 rpm using orbital shaking thermostable incubator (RS-24BL, Remi Instruments Ltd., Mumbai, India). The solutions in the vials were kept for centrifugation in the centrifuge (REMI model C-24 Plus, REMI Electrotechnik Ltd., Vasai, India.) for 20 min at 10,000 rpm. The supernatant solution was then passed through a 0.45µm nylon filter paper and analyzed by the HPLC method.<sup>30</sup>

### Comparative solubility studies

The solubility study was performed by placing plain LUM and SDs in 10 mL of selected dissolution media and water in 20 mL capacity vials and the same procedure was performed as given in the section above.

### In-vitro drug release study

LUM, LUM PM and LUM SDs were accurately weighed equivalent to 120 mg and filled in the hard gelatin capsule (size 000) before the dissolution studies. The *in-vitro* dissolution studies were performed to ensure the quick release of the drug in the dissolution medium using USP type I dissolution apparatus (Electrolab, India) at a speed of 100 rpm. The SDs were compared with the marketed tablet formulation (MAR) (Lumerax DT, Ipca Mumbai). The *in-vitro* dissolution was performed in 0.1 N +HCl 1% Myrj 52 (8.5 mL of HCl was diluted to 100 mL to make 0.1 N HCl). To this solution, 1 g of Myrj 52 was added and the solution was heated on a magnetic stirrer (Remi Instruments Ltd., Mumbai) to give a clear solution. Sample aliquots of 10 mL were drawn at different time points up to 120 min. After each withdrawal, an equal volume of dissolution medium was added to each vessel. The samples were filtered and analyzed by HPLC and the percent drug release at each dissolution time point was calculated. The similarity factor ( $f_2$ ) was calculated for the comparison of various dissolution profiles. If  $f_2$  was  $< 50$ , the dissolution profiles were said to be different and if the  $f_2 > 50$ , then the dissolution profiles had a synchronous or similar release. The equation for the  $f_2$  similarity is given below:

$$f_2 = 50 \cdot \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}, 1 \quad (3)$$

Where n is the number of time points,  $R_t$  and  $T_t$  are the dissolution values for the reference and test batch at time t, respectively.<sup>12,29</sup>

### Fourier Transform Infrared spectroscopy (FTIR) studies

FTIR analysis was performed on samples of LUM, SOL, physical mixture and SD system using KBr respectively. The infrared spectra of samples were obtained from the FTIR spectrophotometer (Model- IR Affinity 1S, Shimadzu, Japan) equipped with an attenuated total reflectance accessory. Each sample analysis included 45 scans, at a resolution of  $4 \text{ cm}^{-1}$  from  $4000$  to  $800 \text{ cm}^{-1}$ .<sup>13</sup>

### Differential Scanning Calorimetry (DSC) studies

The thermal behavior and interaction of pure LUM, physical mixture and SD system were studied using Shimadzu DSC 60 PLUS, Japan. The accurate quantity of samples was crimped in aluminum pans and heated at an increment of  $10^\circ\text{C}/\text{min}$  under nitrogen purge ( $20 \text{ mL}/\text{min}$ ) from  $0^\circ\text{C}$  to  $200^\circ\text{C}$ . Approximately 3 mg of samples were placed in open platinum crucibles which were heated at a heating rate of  $20^\circ\text{C}/\text{min}$ , to temperatures ranging from  $40^\circ\text{C}$  to  $200^\circ\text{C}$  under nitrogen atmosphere ( $50 \text{ mL}/\text{min}$ ). The instrument

was preliminarily calibrated with a standard reference of calcium oxalate. The thermal data obtained were processed using TA60 software.<sup>31</sup>

### X-Ray Diffraction (XRD) studies

The crystalline nature of LUM and solid dispersions were evaluated using X-ray powder diffraction. Diffraction patterns were obtained on Bruker AXS D8 Advance (Germany). The recording spectral was set at  $10^\circ$ - $50^\circ$  ( $2\theta$ ). The parameters like scanning speed, the temperature of acquisition, scintillation counter detector and sample holder were set as  $1/\text{min}$ , room temperature, non-rotating holder respectively. The samples were placed in a zero background sample holder and incorporated on a spinner stage.<sup>19</sup>

### Scanning Electron Microscope (SEM) studies

Scanning electron microscopy is the technique of choice for measuring the shape and surface morphology to support visually the other qualitative and quantitative results. The surface morphology of drug, physical mixture and optimized solid dispersion was studied by using a scanning electron microscope (ZEISS EVO 18, Germany). Double-sided carbon tape was affixed on aluminium stubs over which powder of LUM and prepared SDs was sprinkled separately. The prepared stubs were coated with gold and then were kept in the vacuum chamber. The final adjustment of stubs was done to get high-quality images.<sup>18</sup>

### In-vitro antimalarial assay

The plain drug LUM and the optimized SD were tested for *in vitro* antimalarial activity against *Plasmodium falciparum* 3D7. The *in-vitro* cultures of Chloroquine - sensitive (3D7) strain of *P. falciparum* was routinely cultured in medium RPNI supplemented with 25mM HEPES, 0.2% D-glucose, 0.21% sodium bicarbonate and 0.5% ALBUMAX-II. The stock solution (5.0 mM) of compounds prepared in DMSO was used. The required dilutions were made in the culture medium. For evaluation of 50% Inhibitory concentration ( $\text{IC}_{50}$ ) of the compounds, Malaria SYBR Green I-based fluorescence (MSF) assay was carried out.

### Assay technique

The highest concentration of test samples was  $5.0 \mu\text{M}$ . Subsequent two-fold serial dilutions were made in 96 well-plate and incubated with 1.0% parasitized cell suspension containing 0.8% parasitemia (Asynchronous culture with more than 80% ring stages). The plate was incubated at  $37^\circ\text{C}$  in a  $\text{CO}_2$  incubator in an atmosphere of 5%  $\text{CO}_2$  and air mixture. After 72 hrs,  $100 \mu\text{L}$  of lysis buffer containing 2x concentration of SYBR Green-I

(Invitrogen) was added to each well and incubated for one hour at 37°C. The plate was examined at 485±20nm of excitation and 530±20nm of emission for relative fluorescence units (RFUs) per well by using a fluorescence plate reader (FLX800, BIOTEK). The IC<sub>50</sub> values were obtained by Logit regression analysis of dose-response curves. Chloroquine diphosphate (SIGMA) was used as the reference drug.

### In-vitro cytotoxic activity

Cytotoxicity of test samples (Plain LUM and optimized SD) was carried out using Vero cell line (C1008; Monkey kidney fibroblast cells). The cells were incubated with test sample dilutions for 72 h and MTT was used as a reagent for the detection of cytotoxic activity. The highest concentration of test samples used was 200µM. The 50% cytotoxic concentration (CC<sub>50</sub>) was determined using dose-response curves. Podophyllotoxin (SIGMA) was used as the reference drug. Selectivity Index (SI) can be calculated as:  $SI = CC_{50} / IC_{50}$  and criteria for selection is:  $SI = >50.0$ .<sup>32,33</sup>

### Moisture Uptake and Stability Studies

Moisture uptake study was carried out to check the hygroscopic nature of the optimized SD. LUM is hygroscopic and it thus helped to determine the degradation effect of the moisture entrapped by these drugs. Moisture uptake and stability studies were conducted by placing the weighed amount of SD in capped glass vials wrapped in an aluminum foil and placed in a stability chamber (Biotechnics, India.) maintained at a temperature of 40 ± 2°C and humidity condition at 75±5% RH and at room temperature. Samples were removed after 3 months and change in weight of samples was determined using digital weighing balance along with the *in-vitro* release study of the SD.<sup>29</sup>

### Statistical analysis

The Mann-Whitney U test with statistical significance ( $p < 0.05$ ) was applied to the dissolution data using Graphpad Prism version 5. The Gibbs free energy, Florey-Huggins parameter and  $f/2$  calculations were performed using the Microsoft Excel sheet 2010. Descriptive analysis, including mean and standard deviation, was used to evaluate numerical data.

## RESULTS AND DISCUSSION

### Analytical method

The retention time of LUM was 12.987 min (Figure 1). A calibration curve was obtained by plotting the area of absorbance peak (recorded from the injection of

known quantities) as a function of concentration and the data was modeled using a linear regression equation. A correlation coefficient of 0.9985 was obtained with the equation  $y=15053x-49497$ .

### Evaluation of solubility parameter

The value of the solubility parameter ( $\delta$ ) of LUM was compared with the solubility parameter ( $\delta$ ) of different hydrophilic polymers (Table 1). The difference in solubility parameters ( $\Delta\delta$ ), between the LUM and hydrophilic polymers, of less than 7 MPa<sup>0.5</sup> results in miscibility between them. Therefore, polymers with the least  $\Delta\delta$ , namely Soluplus, Kollidone VA 64, Poloxamer 188 and Plasdone S630 were chosen for the studies. The results showed that Soluplus had  $\Delta\delta$  value closer to 1 which is significantly below 7 MPa<sup>0.5</sup>, symbolized higher miscibility with LUM that may lead to the greater physical stability of the solid dispersion.<sup>22,28</sup>

### Solubility studies for the selection of dissolution media

The drug was found to be practically insoluble in water following the previous literature,<sup>21</sup> but soluble in 0.1 N

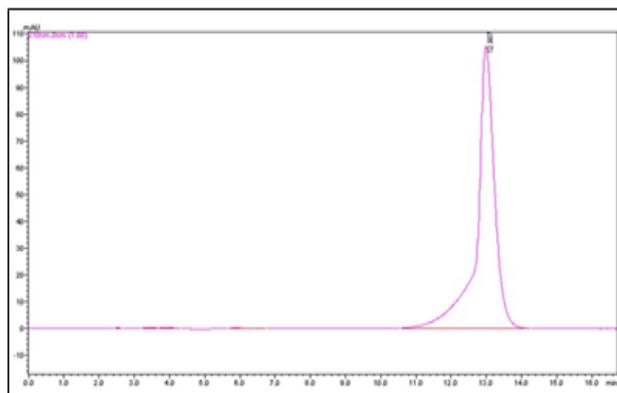


Figure 1: Chromatogram of LUM in the mobile phase.

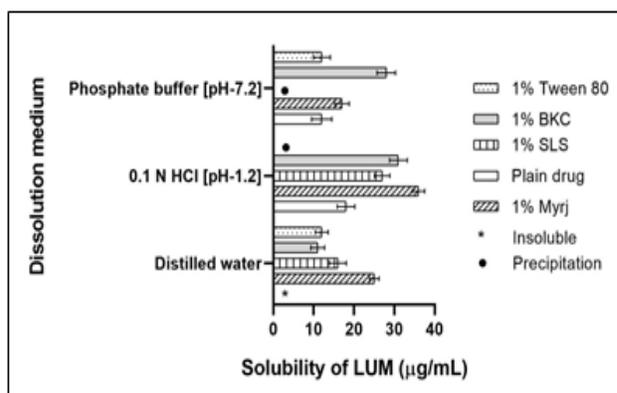


Figure 2: Solubility of Lumefantrine in different solvent media alone and with various surfactant.

HCl pH 1.2 and phosphate buffer pH 7.2 as shown in Figure 2. When the surfactant was added to the water, 0.1 N HCl and phosphate buffer increased solubility of the drug was found. Thus, to maintain the sink conditions, increase the saturation solubility and wetting of the drug, surfactants were added. The precipitation was observed between 1% SLS and phosphate buffer and between 1% Tween 80 and 0.1 N HCl. Hence, these two systems were rejected. The two surfactants 1% BKC and 1% Myrj 52 showed quite a good solubility for the drug in all three dissolution media. Higher solubility was observed for 1% Myrj 52 as compared to 1% BKC. The stability of storage was also checked for 48 hrs. And then it was found that 0.1 N HCl + 1% Myrj 52 was quite stable for the mentioned duration. While in phosphate buffer + 1% BKC there was the deposition of whitish particles on storage thus it was inferred to be unstable for HPLC analysis.

### Preparation of solid dispersion

The solvent evaporation method involves the evaporation of the solvent in a controlled manner that leads to a uniform distribution of particle size and coats the drug with a polymer. This converts the drug from crystalline to amorphous nature. The rotary evaporation is a simple and single-step process, thus avoids ambiguity. The process parameters like temperature and rpm can be controlled with ease. Solvent evaporation using a rotary evaporator was used because it was economical, safe

for the environment and thermal degradation of LUM was prevented.<sup>18</sup> Considering these factors, the rotary evaporation method was much favorable. For preparing SDs, various solvents (methanol, ethanol, acetonitrile, ethyl acetate and acetone) were tried to dissolve the drug and SOL simultaneously. The final solvent selected was chloroform as it was able to dissolve both the components. In this method, evaporation of the solvent (Chloroform) containing drug and SOL was carried out under reduced pressure and low temperature. The composition of the SDs are given in Table 2.

### Gibbs free energy $\Delta G^{tr}$ and Florey-Huggins interaction parameter ( $\chi$ )

The Gibbs free energy  $\Delta G^{tr}$  value of SDs was calculated (Table 2), where all the SDs were found to be negative indicating that the two components favored miscibility. The good miscibility resulted in stable SDs and can also be said to improve the dissolution rate. As the concentration of SOL increased the  $\Delta G^{tr}$  values decreased. If  $X \geq 0.5/M$  then there is a presence of unfavorable interactions between the drug and polymer.<sup>29</sup> As shown in Table 2, the value of X for all the SDs was found to be not more than or equal to 0.5/M. This can be due to the formation of dispersion at the molecular level with reduced entropy favoring the mixing of LUM and SOL. The strong adhesive interaction between LUM and SOL was favored by the reduction in the temperature of the mixture in the SD system that represented the miscibility of LUM and SOL. Thus, indicated that the formulated solid dispersions were thermodynamically stable.

### Comparative solubility studies

The study revealed that the solubility of LUM SDs was found to be higher in 0.1 N HCl (pH 1.2) + 1% Myrj 52 than that of water as shown in Figure 3. As the concentration of SOL increased in the SDs, significant increase in the drug solubility was observed. The micellar solubilization phenomenon of SOL can be the possible reason for the increment in solubility. While preparing the SDs, care was taken to keep the concentration of

**Table 1: Solubility parameter of lumefantrine and various carriers based on the Van Krevelen-Hoftyzer method.**

Drug/polymer	Van Krevelen-Hoftyzer method MPa <sup>0.5</sup>	$\Delta\delta$ MPa <sup>0.5</sup>
Lumefantrine	24.55	-
Soluplus	23.12	1.43
Plasdone S630	22.94	1.61
Kollidone VA 64	22.55	2.00
Poloxamer 188	20.32	4.23

**Table 2: Composition of SDs, Gibbs free energy and Florey-Huggins interaction parameter calculation and solubility of SDs in water and 0.1 N HCl + 1% Myrj 52.**

SD code	LUM: SOL ratio	Gibbs free energy $\Delta G^{tr}$	Florey-Huggins interaction ( $\chi$ )	Solubility of SD in water ( $\mu\text{g/mL}$ )	Solubility of SD in 0.1 N HCl + Myrj 52 ( $\mu\text{g/mL}$ )
L1	1:1	-24832.86	$29.88 \times 10^{-5}$	$27 \pm 5.1$	$135 \pm 3.3$
L2	1:2	-25330.12	$7.47 \times 10^{-5}$	$33 \pm 2.2$	$182 \pm 3.1$
L3	1:3	-25927.73	$3.32 \times 10^{-5}$	$42 \pm 4.1$	$211 \pm 5.1$

Values expressed as mean  $\pm$  SD, n=3 for SD solubility.

SOL above its critical micellar concentration (0.0007% w/v).<sup>17</sup> The increase in solubility in both water and 0.1 N HCl (pH 1.2) + 1% Myrj 52 could probably be elucidated by the creation of a hydrophilic environment around the LUM that resulted in decreased particle size and increased wettability of LUM. The increase in solubility of the SDs may be a result of conversion from crystalline to amorphous form due to the amorphous nature of the SOL. The crystalline nature of the drug hinders solubility as well as dissolution because the crystal needs to be broken down first and then the drug goes into the solution. As the crystal structure is found to be quite ordered, the thermodynamic energy barrier is lowered when crystalline drug converts into an amorphous form. The disordered structure in amorphous form, therefore, bypasses the lattice breaking step and efficiently aid in solubilization and dissolution. The SOL dissolved in a better way in 0.1 N HCl than in water. It can be because of the decreased pH at the solid-liquid interface as a result of the protonation of various OH groups present in the SOL. When the SOL goes into the selected dissolution media, there is also the release of the drug from the SOL matrix. This event retards the inner core SOL from dissolving and thus faster drug solubilization and dissolution may take place.

### In-vitro dissolution study

*In-vitro* release tests were performed under the sink condition to evaluate the drug release from the SDs in 0.1 N HCl + 1% Myrj 52. The release of LUM from all SDs was plotted as a cumulative percent drug release versus time in minutes as shown in Figure 4. More than 50% of the drug was dissolved out of SDs within 20 min while it was just 10% in the case of pure drug. At the end of 120 min, approximately 70% of the LUM was released from all the SDs. The dissolution rate of pure LUM was observed to be very slow (42.56 %) as compared to the

PM (65.23%), Marketed tablet (58.11%), L1 (73.56%), L2 (90.23%) and L3 (84.18%). The similarity ( $f_2$ ) factor was calculated from the dissolution data for the comparative studies are depicted in Table 3. There was an increment in the dissolution rate of PM as compared to plain drug and marketed tablet with statistical significance of  $f_2 < 50$  (PM / LUM = 29.06 % and PM / Marketed tablet = 40.50%). Similarly, increment in the dissolution rate of the marketed tablet as compared to plain LUM was observed with the statistical significance of  $f_2 < 50$  (LUM / MAR = 45.44%). From all the  $f_2$  values, it can be concluded that the dissolution profiles of all the components are different from each other. The slow dissolution of LUM might be from the crystalline form that has poor aqueous solubility. The dissolution profile of L2 shows higher dissolution as compared to that of L1, L3, physical mixture and plain drug. The surfactant property of the carrier decreases the interfacial tension between the medium and the drug, providing good dissolution. The statistical data after applying the Mann-Whitney U test on the dissolution data of all the components are shown in Table 4. It can be inferred that there was a significant difference between the dissolution profile of plain drug and SDs. Also, there was a significant difference between the marketed tablet's dissolution profile and the SDs.

### FTIR studies

FTIR spectra of the characteristic peaks of LUM, SOL, physical mixture of drug with SOL and SD of the optimized batch were studied (Figure 5). FTIR spectrum of LUM presented characteristic peaks at OH stretch ( $3200-3600\text{ cm}^{-1}$ ) at 3398.70. The C-H stretching ( $2850-3000\text{ cm}^{-1}$ ) was observed at 2949.16, C=C stretching ( $1620-1680\text{ cm}^{-1}$ ) at 1635.64, aromatic C-H stretching ( $3000-3100\text{ cm}^{-1}$ ) at 3089.96, aromatic C=C stretching ( $1400-1600$ ) at 1487.12, C-O (alcohol) stretching ( $1050-$

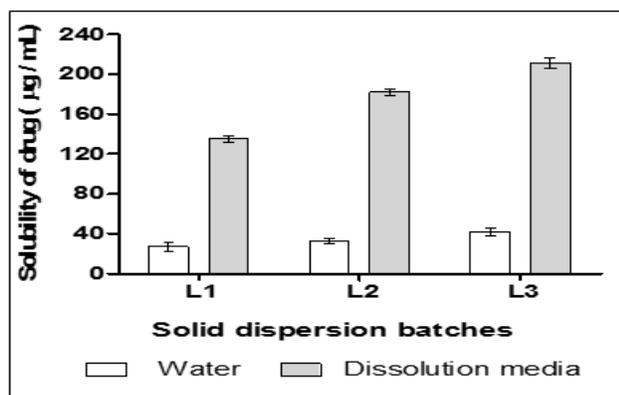


Figure 3: Comparison of LUM with SD in water and dissolution media, Values expressed as mean  $\pm$  SD,  $n=3$  for SD solubility.

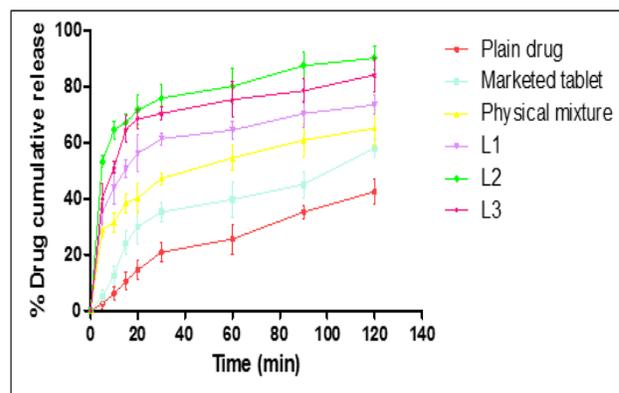
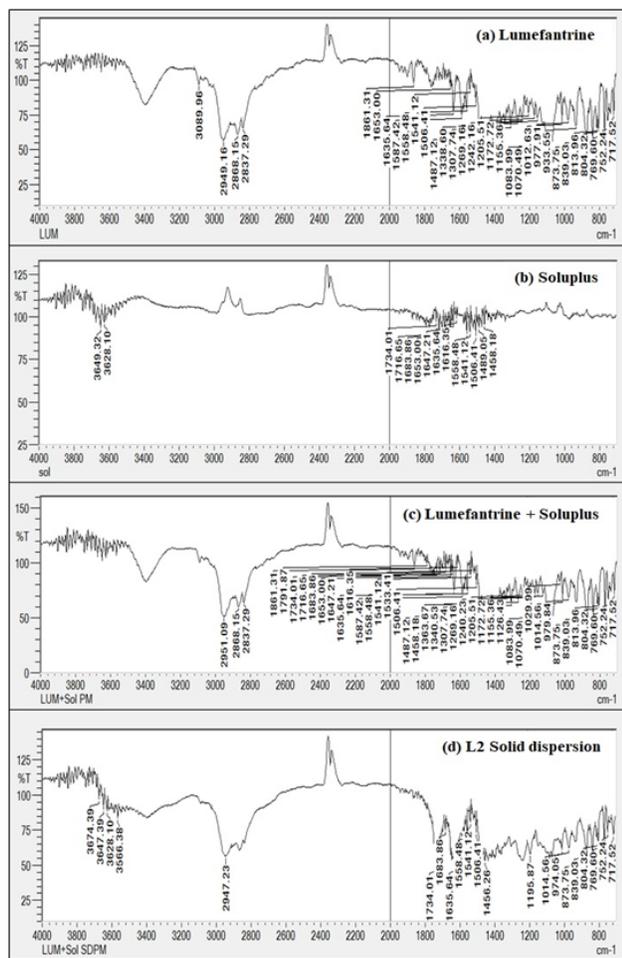


Figure 4: Dissolution profile of LUM in different formulations, Values expressed as mean  $\pm$  SD,  $n=3$ .

**Table 3: Similarity factor f2 values of each two of the release profiles.**

SD / LUM	f2 (%)	SD / PM	f2 (%)	SD / MAR	f2 (%)
L1 / LUM	21.33	L1 / PM	46.88	L1 / MAR	29.09
L2 / LUM	31.17	L2 / PM	27.57	L2 / MAR	18.34
L3 / LUM	16.28	L3 / PM	33.51	L3 / MAR	22.36

1150 cm<sup>-1</sup>) at 1070.49, C-Cl stretching (600-800 cm<sup>-1</sup>) at 769.60, C-N stretching (1080-1360 cm<sup>-1</sup>) at 1083.99. Observed values were found within the range of standard values of LUM. FTIR spectra of SOL exhibited various peaks for C=C aromatic stretching (1580-1600 cm<sup>-1</sup>) and the free OH stretching (3500-3800 cm<sup>-1</sup>) at 3649.32. It showed a broad peak at 3000–3500 cm<sup>-1</sup>, owing to the presence of -OH stretching groups. SOL also showed peaks at 1734.01 (ester linkage), 1616.35 (amide linkage). The spectrum of the physical mixture was equivalent to the addition of the spectrum of the LUM and SOL suggesting no interaction occurring in physical mixing. The LUM spectrum was not affected chemically by the

**Figure 5: FTIR spectrum of (a) LUM, (b) SOL, (c) LUM+SOL physical mixture and (d) SD L2.**

presence of SOL which means that the components of the SD system were compatible. Thus, the LUM and SOL were compatible. The spectra of L2 represents the presence of LUM with no alteration in the functional property on forming the SD system. For L2, the OH stretching band was broadened with decreased intensity prompting interaction between proton donating and proton accepting group of LUM and SOL respectively. SOL has hydrophilic groups which aid in the dissolution of the LUM and thus quick release from SD may have resulted as obtained in the *in-vitro* release study. Slight shifts in the characteristic peaks was observed of LUM and SOL as a result of the formation of molecular dispersion due to the hydrogen bonding between LUM and SOL's hydroxyl groups. Thus, preventing crystallization tendency and kept the LUM in molecular dispersed state into the SOL matrix. The drug was intact and there was no sign of degradation as the solvent evaporation technique was used. It can also contribute to the significant increase of dissolution of the LUM SDs in comparison to the pure LUM.

### DSC studies

Differential scanning calorimetry was performed to determine the melting point and the nature of the drug in the SD. Figure 6 represents the DSC thermographs of the plain drug, physical mixture of drug and SD of drug respectively. The SOL does not show any endothermic peak due to the amorphous nature. Pure LUM showed a sharp endothermic peak at 131.23°C with an enthalpy of 91.25 J/g while in physical mixture showed a small endothermic peak at 130.2°C with an enthalpy of 28.47 J/g. The molecular interaction between the LUM and the SOL resulted in the formation of the glassy solid solution i.e., SD. The drop in enthalpy from 91.95 J/g (LUM) to 28.47 J/g (physical mixture) and from 28.37

**Table 4: Results of the Mann-Whitney U test.**

Comparison components	Mann-Whitney U	Two-tailed p-value	Significant difference in medians (p<0.05)
L1 vs. LUM	2	0.0006	Yes ***
L2 vs. LUM	0	0.0002	Yes ***
L3 vs. LUM	1	0.0003	Yes ***
L2 vs. PM	4	0.0019	Yes **
L3 vs. PM	8	0.0104	Yes *
L1 vs. L2	10	0.0207	Yes *
L1 vs. MAR	8	0.0104	Yes *
L2 vs. MAR	1	0.0003	Yes ***
L3 vs. MAR	3	0.0011	Yes **
PM vs. LUM	6	0.0047	Yes **

J/g to 18.18 (L2) shows a gradual decrease pattern emphasizing the fact that interaction could be present in the physical mixture as well as in the L2. Also, the decrease and shifts of the LUM melting event suggested interaction between LUM and SOL. Short ranged interactions such as hydrogen bonding and Van der Waals forces may be the possible reason. The results are in agreement with the FTIR studies. The absence of the sharp melting endotherm in the thermogram of L2 indicated transformation of LUM from crystalline to the amorphous state. The less intense peak of LUM suggested the interaction with SOL which attributed to the increased dissolution.

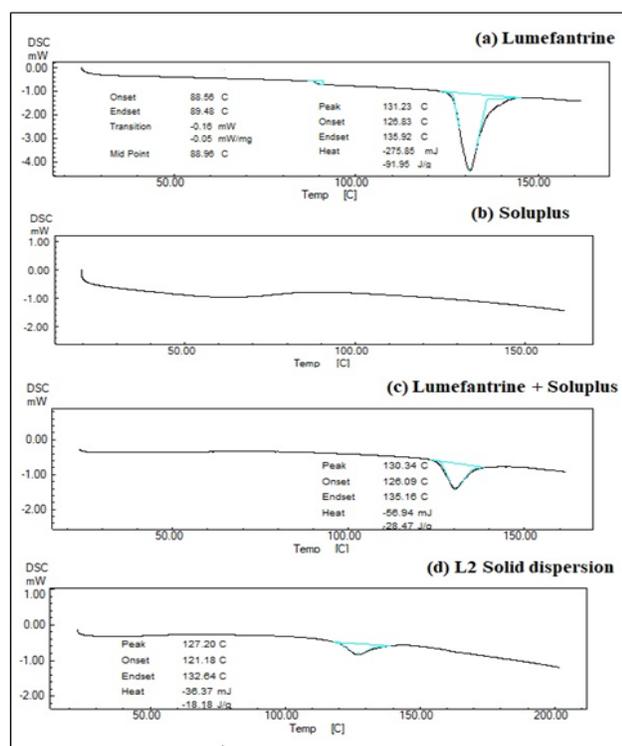
### XRD studies

XRD diffraction patterns (Figure 7) of pure LUM revealed the crystalline nature with intense peaks at  $2\theta$  of  $5.541^\circ$  with Lin (Counts) = 70,000 and other peaks at  $2\theta$  of  $11.112^\circ$ ,  $14.963^\circ$ ,  $18.063^\circ$ ,  $18.577^\circ$ ,  $20.152^\circ$ ,  $20.997^\circ$ ,  $22.343^\circ$ ,  $23.089^\circ$ . In the case of L1 diffraction peaks were at  $2\theta$  of  $5.751^\circ$  with Lin (Counts) = 7,100 and other peaks at  $2\theta$  of  $11.318^\circ$ ,  $15.184^\circ$ ,  $18.299^\circ$ ,  $20.355^\circ$ ,  $21.215^\circ$ ,  $21.755^\circ$ ,  $22.162^\circ$ ,  $23.292^\circ$ ,  $25.618^\circ$  and  $27.264^\circ$ . In the case of L2 (1:2), the characteristic diffraction peak disappeared and other peaks at  $2\theta$  of  $9.880^\circ$ ,  $10.539^\circ$ ,  $11.606^\circ$ ,  $14.330^\circ$ ,  $18.002^\circ$ ,  $19.616^\circ$  and  $23.171^\circ$  were observed. In case of L3 diffraction peaks

was at  $2\theta$  of  $5.809^\circ$  with intensity count = 4,400 Lin (Counts) and other peaks at  $2\theta$  of  $11.331^\circ$ ,  $15.215^\circ$ ,  $18.318^\circ$ ,  $20.375^\circ$ ,  $21.240^\circ$ ,  $23.319^\circ$ ,  $25.646^\circ$ ,  $27.291^\circ$  and  $28.516^\circ$ . XRD diffractogram of SDs showed decreased crystalline nature which decline in the intensity of the peak. The new peaks found in the case of all SDs suggested physical interaction between the LUM and the SOL, which led to modifications in the crystalline structure of LUM. The relative drop in the diffraction intensity (from Lin (counts) = 70,000 to 4,400) of LUM in SDs suggested that the crystalline status of LUM changed because of SOL, with high content of SOL as a result the peaks broadened slightly, with a partial loss of LUM peaks due to the interaction with the SOL. All SDs showed a similar diffractogram as of pure LUM and had low intensity peaks, suggesting the crystallinity of SDs of L1, L2 and L3 decreased during the drying process by solvent evaporation. The intense peak of LUM at a  $2\theta$  value of  $5.541^\circ$  may have shifted significantly in the diffractogram of L2 revealing stronger interaction with SOL. The diffractograms of the SDs varied owing to the change in the SOL to LUM ratios. The data also corresponds with the DSC studies.

### SEM studies

Photomicrographs of free LUM, physical mixture of LUM and L2 were studied for the morphological characteristics using SEM as represented in Figure 8. Photographs of LUM showed typical large crystals of non-uniform sizes. The sharp-edged drug particles were observed. The SOL is amorphous and showed irregular spherical shaped particles with the presence of LUM as rough particles in the physical mixture. The L2 appeared as a homogenous, agglomerated solid fused mass. The surface property of LUM was transformed may be due to crystalline to amorphous transformation. The genuine LUM crystals disappeared in the L2 SD SEM image. The LUM was changed dramatically after L2 SD formation because of the treatment with the SOL. The analysis confirmed that LUM was deposited on the SOL in L2 SD. This may be due to the interaction between the LUM and SOL. The LUM crystals were coated completely and uniformly by the SOL that prevented the recrystallization of LUM from L2 SD. The formed SD L2 depicted the existence of LUM in a micro amorphous form with a reduced particle size with increase in surface area and had intimate contact with the SOL. Owing to this, there was an enhancement in solubility and improvement in the dissolution rate. Significant changes occurred in the geometry and topographical surface of the crystal during the solvent evaporation process.



**Figure 6: Thermogram of (a) LUM, (b) SOL, (c) LUM+SOL physical mixture and (d) SD L2**

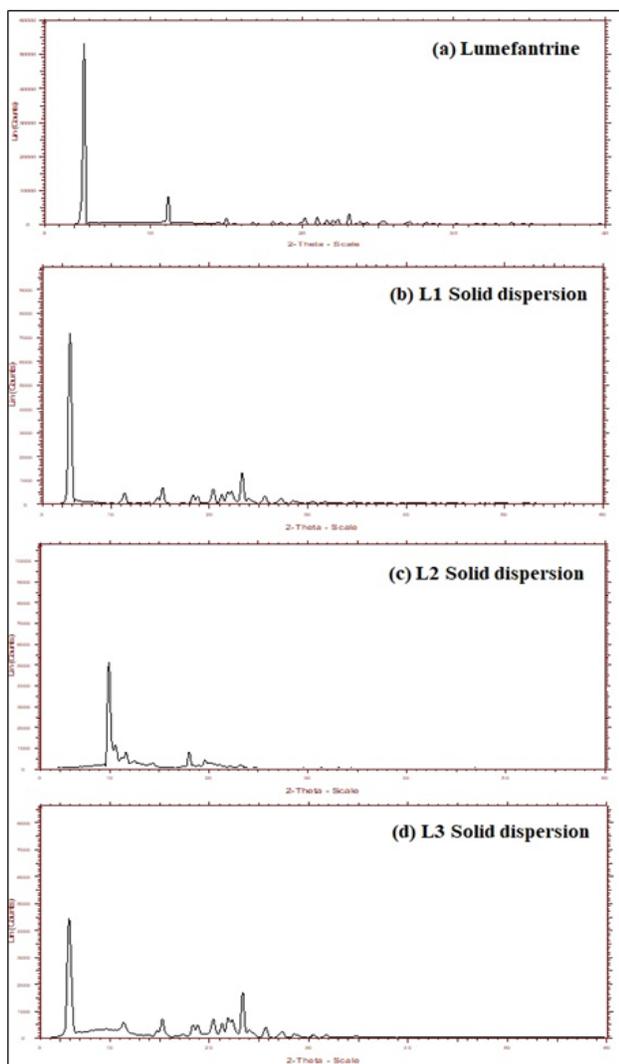


Figure 7: XRD diffractograms of drug (a) LUM, (b) L1, (c) L2, (d) L3.

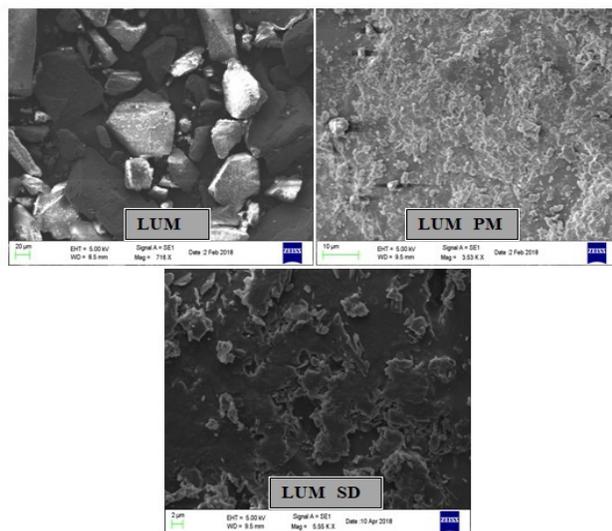


Figure 8: SEM microscopic images of drug LUM, LUM PM and LUM SD.

Table 5: *In-vitro* activity against *Plasmodium falciparum* 3D7 and *in-vitro* cytotoxic activity using the Vero cell line.

Sample	IC <sub>50</sub> (ng/mL) Pf3D7	CC <sub>50</sub> (µg/mL) against the Vero cell line
LUM	18.2	>500
L1	8.36	>500
L2	3.37	>500
L3	10.54	>500
Chloroquine	1.73	365.6

Table 6: Moisture uptake studies and stability study of L2.

Evaluation parameter	0 day at room temperature	3 months at room temperature	3 months at 40°C 75% RH
Appearance	No color change	No color change	No color change
Weight of L5	98.96±1.2 mg	98.95±0.9 mg	98.94±1.1 mg
<i>In-vitro</i> drug release %	90.12±2.25	89.95±2.11	89.12±1.36

#### *In-vitro* antimalarial assay

The *in-vitro* antimalarial activity showed that L2 at small concentrations was active against *P. falciparum* 3D7 than L1 and L3. The IC<sub>50</sub> value of standard antimalarial drug, Chloroquine was 7 times higher than that of L2 while IC<sub>50</sub> value of LUM was 4 fold higher than L2. The results are shown in Table 5.

#### *In-vitro* cytotoxicity assay

The CC<sub>50</sub> value of all SDs was observed and compared with LUM (Table 5). Cytotoxic activity on Vero cell lines thus, showed a selectivity index of >50 for all SDs indicating non-toxicity. It was observed that all SDs decreased the toxicity in monkey kidney cells compared to the standard drug Chloroquine. Cytotoxic activity on Vero cell lines showed non-toxicity of SDs.

#### Moisture uptake and stability study

The moisture uptake study revealed that there was no statistically significant change in the weight of the L2 powder. In the case of L2, the moisture content was indicative of the interaction and degree of mixing of LUM with SOL as a matrix polymer. The range (1.02±0.23 to 2.37±0.24%) of moisture content does not exceed which indicated no degradation occurred in the L2.<sup>29</sup> The accelerated stability study revealed no considerable change in appearance of L2 during the study period. The *in-vitro* drug release % for L2 was found to be almost the same as the initial. The data of both studies are shown in Table 6.

## CONCLUSION

In this study, the use of SOL to enhance the solubility of LUM was employed. A significant increase in solubility which was dependent on concentration of SOL was observed. LUM SDs formulated by the solvent evaporation method produced an enhancement in drug solubility. LUM was transformed from crystalline state to the amorphous state using SOL as a hydrophilic carrier. A significant increase in the dissolution rate was achieved through SDs and immediate release of LUM from SD was observed. Solubility studies showed improvement in the solubility of the drugs. The dissolution profile was improved as compared to the plain drug. The in-vitro antimalarial assay of LUM SD showed efficacy and was also non-cytotoxic. Hence, the LUM SD L2 had superiority over plain LUM in terms of the solubility, dissolution rate and antimalarial efficacy.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

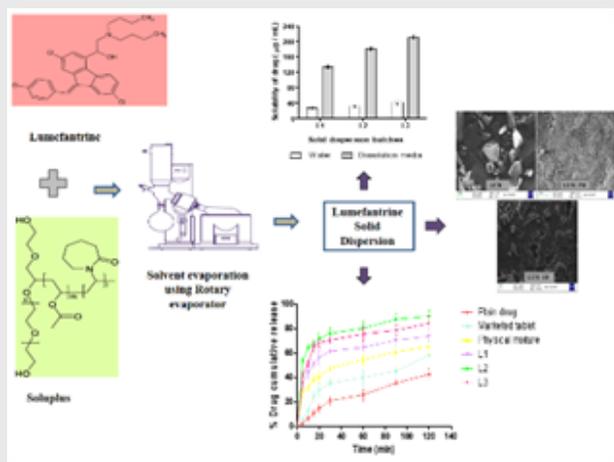
**LUM:** Lumefantrine; **SOL:** Soluplus; **PM:** Physical mixture; **MAR:** Marketed tablet; **SD:** Solid dispersion; **SLS:** Sodium Lauryl Sulphate; **BKC:** Benzalkonium chloride; **DSC:** Differential scanning calorimetry; **FTIR:** Fourier transformed infrared spectroscopy; **HPLC:** High-performance liquid chromatography; **SEM:** Scanning electron microscopy; **XRD:** X-ray diffraction.

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## PICTORIAL ABSTRACT



## About Authors



**Miss. Pranita Sunil Kanojiya**, She is a Ph. D. research scholar (CSIR Junior Research Fellow) at the Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, INDIA.



**Miss. Yogita Charde**, She is working as an Assistant Professor at Sai Nath College of Pharmacy, Nagpur, Maharashtra, INDIA.



**Dr. Jasmine Gev Avari**, She is working as a Professor and HOD of the Department of Pharmaceutical Sciences, Rastrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, INDIA.



**Dr. Rita Wadetwar** She is working as an Assistant Professor at the Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, INDIA.

## SUMMARY

The antimalarial drug Lumefantrine is poorly soluble and to enhance the aqueous solubility, solid dispersion was formulated using Soluplus by solvent evaporation under reduced pressure using a rotary evaporator. The method allowed the removal of solvent completely from the solid dispersion, hence it was chosen. The dissolution media was selected among various solvents. The optimized media used was 0.1N HCl + 1% Myrj 52. The solubility study was performed using HPLC. The feasibility of solid dispersion was studied by using the solubility parameter ( $\delta$ ). The prepared solid dispersions were evaluated for DSC, SEM, FTIR and XRD. The DSC and FTIR confirmed the compatibility between the components of the solid dispersion. Also, the crystalline form was transformed to the amorphous form as confirmed by the XRD. The SEM studies demonstrated the change in morphology of the drug from sharp crystals to the homogenous mass in the solid dispersion. The aqueous solubility of L2 was found to be  $135 \pm 3.3 \mu\text{g/mL}$  using the selected dissolution media which was completely insoluble in comparison to the plain drug. The *in-vitro* dissolution studies showed release of optimized batch L2 with a maximum release of 90.23% in comparison to the marketed tablet with a release of 58.11%. The *in-vitro* antimalarial screening was performed using *P. falciparum* 3D7 strain showed the efficacy of the L2 and *in-vitro* cytotoxicity study was performed using Vero cell line which demonstrated the safety of all the solid dispersions. The stability study was carried out for 3 months and resulted in good stability of L2.

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