

# Solid Dispersion of Artemether in Fast Disintegrating Tablet to Enhance Dissolution Rate and Oral Bioavailability

Pranita Sunil Kanojiya\*, Yogita Manohar Charde, Rita Naresh Wadetwar

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

## ABSTRACT

**Objectives:** Artemether (ART), an antimalarial drug, have poor solubility and low bioavailability. Therefore, solid dispersion of the drug was formulated using Soluplus (SOL) and was incorporated in the fast disintegrating tablet. **Materials and Methods:** The solid dispersion (SD) was prepared using the solvent evaporation method using a rotary evaporator. The optimized SD was evaluated and then incorporated into the tablet. **Results:** Solubility studies revealed that ART SD A3 of ratio 1:3 (ART: SOP) showed a significantly higher solubility and dissolution rate than plain ART. FTIR results indicated that there was no incompatibility between the drug and hydrophilic carrier. The DSC as well as XRD studies indicated the transformation from crystalline state of drug into the amorphous form. SEM studies revealed the deposition of ART on the surface of the hydrophilic carrier. *In-vitro* antimalarial activity was improved of the ART due to the SD formulation. Fast disintegrating tablet of ART SD A3 was produced by using directly compressible excipients such as Ludiflash and Ludipress. Ludiflash containing tablet showed fast disintegration with higher drug release. The pharmacokinetic study in mice showed increased  $C_{max}$  and  $AUC_{0-24}$  by 1.88- and 3.19-fold as compared to those of plain drug. **Conclusion:** The prepared SDs using SOP provided a platform for increased solubility and also improved the bioavailability of ART with feasibility for tablet formulation.

**Key words:** Artemether, Solid dispersion, Fast disintegrating tablet, Malaria, *in-vivo* study.

**Key message:** The Artemether solubility was improved with the Soluplus by preparing solid dispersion and used in fast disintegrating tablets resulting in enhancement of the bioavailability after oral administration.

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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 – kanojiyaprani06@gmail.com

## INTRODUCTION

Drugs have low bioavailability due to poor aqueous solubility or due to erratic absorption. Due to the solubility issues of drugs, it is estimated that 40% of the NCE (New chemical entity) are deprived to have the status of the marketed drug though these NCE have promising pharmacodynamic effects.<sup>1</sup>

Malaria is caused due to the parasite of *Plasmodium* spp. transmitted by mosquitoes' bite to the human and conceived through the blood causing infection. Artemisinin represents a vital class of antimalarial drugs

that contains sesquiterpene lactone having a bridge of peroxide. Artemether is one of the potent drug which is quite effective in cases of multidrug-resistant strains of the parasite and thus enlisted in the WHO's list of essential medicines.<sup>2</sup> The drug shows activity against *P. falciparum* strain of both Chloroquine sensitive and Chloroquine-resistant and also active against *Plasmodium vivax*. The drug breaks the life cycle of the malarial parasite resulting in the inhibition of parasite multiplication. The potential effect of the drug hinders due to the poor



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bioavailability resulting from poor aqueous solubility of the drug.<sup>3,5</sup>

The design of an oral formulation containing a poorly soluble drug is very tough and also it should be efficient with safe profile. The main challenge lies in improving the solubility of such drugs and then formulating the same in a suitable dosage form.<sup>6,7</sup> The widely used method for increasing the aqueous solubility of the poorly soluble drug is formulating the solid dispersion.<sup>8</sup> The solid dispersion consists of the combination of a poorly soluble drug or active pharmaceutical ingredient with a hydrophilic polymer or carrier either alone or in the combination of two polymers.<sup>9,10</sup> In the solid dispersion, the active molecule is uniformly dispersed at the molecular level within the carrier matrix and thus improves the solubility, dissolution rate and physical stability.<sup>6</sup>

Soluplus® is a graft co-polymer consisting of polyvinyl caprolactam, polyvinyl acetate and polyethylene glycol. Recently, it is an extensively utilized polymer for the solubility enhancement of poorly soluble drugs for the preparation of the solid dispersions.<sup>11-13</sup> It is amphiphilic and thus can be effectively used as a solubilizer and as a carrier matrix. Soluplus has shown promising solubilization effect in the case of BCS class II and IV drugs. The dissolution rate enhancement by formulating the solid dispersion of the drug having poor aqueous solubility using Soluplus can be a beneficial approach.<sup>2,14</sup> The poor solubility issue of the drug can be resolved by the use of a combination of methods for the increase in oral bioavailability such as preparing the solid dispersion and then adding the same into a fast disintegrating tablet.<sup>7,15</sup> The fast disintegrating tablet is a viable option to ascertain the solubility issue.<sup>16</sup> The use of fast disintegrating tablets for the solubility enhancement can add more benefit for the solid dispersion such as provide faster disintegration and promote quick release of solid dispersion resulting in enhanced dissolution thereby improving the oral bioavailability.<sup>17</sup> The method for the formulation of the tablets include wet granulation, direct compression, spray drying, freeze-drying and molding. The direct compression method is more economic, industrially feasible and time-saving.<sup>18,19</sup>

For the treatment of malarial infection, the drug must achieve a therapeutic level in the systemic circulation that is only possible when the drug dissolution rate is improved. The present research work can overcome the bioavailability issue of the Artemether by first formulating its solid dispersion using Soluplus and then incorporating the same into a fast disintegrating tablet to achieve the goal by the administration through

oral route. To date, there is no literature available for the formulation of the Soluplus -Artemether solid dispersion incorporated in fast disintegrating tablet with the characterization of the formulation for solubility, dissolution, antimalarial activity and bioavailability. The study aimed to formulate and characterize the Artemether-Soluplus solid dispersion prepared by kneading method and solvent evaporation method. The dispersion with high solubility was selected for the direct compression into the fast disintegrating tablet by employing novel excipients and evaluated for the *in-vitro* studies. The performance of the optimized tablet was investigated by the *in-vivo* pharmacokinetic study in mice.

## MATERIALS AND METHODS

ART and Myrj 52 were generously gifted by Mangalam Drugs and Organics Ltd., Mumbai and Mohini Organics, Mumbai respectively. Soluplus, Kollidone VA 64, Ludiflash and Ludipress were kind gifts from BASF (Mumbai, India). Plasdone S 630 was a gift sample from Ashland, Hyderabad. Potassium dihydrogen orthophosphate, Sodium Hydroxide were purchased from S. D. Fine Chemicals India. Methanol, Water, and Acetonitrile (HPLC grade) were procured from Merck Specialties Pvt. Ltd., Mumbai. Orthophosphoric acid, Hydrochloric acid, Acetone and Triethylamine were purchased from Loba Chemie, Mumbai. All solvents used for the HPLC system were of HPLC grade. Chloroquine diphosphate and Podophyllotoxin were purchased from Sigma Aldrich (India).

### Phase solubility study

The excess of the ART was added into 10 mL of 0.1 N HCl+ 0.5% Myrj 52 with hydrophilic carriers such as Soluplus, Kollidone VA 64, and Plasdone S 630 (1-10% w/v) in a glass vial separately. The sample solutions were sonicated (Ultrasonicator, PCi, Mumbai, India) for 20 min (at ambient temperature), and kept for shaking for 48 h at  $37 \pm 0.10^\circ\text{C}$  at a speed of 75 rpm using orbital shaking thermostable incubator. After 48 h, the solution was centrifuged (REMI model C-24 Plus, REMI Electrotechnik Ltd., Vasai, India) at 10,000 rpm for 20 min and then filtered utilizing a membrane filter (0.45  $\mu\text{m}$ ) and analyzed through spectrophotometry (UV-1700, Shimadzu, Japan) at 210 nm for the drug solubility.<sup>11,20</sup>

### Preparation of ART solid dispersion

#### Kneading method

The physical mixture of ART+SOP in various ratios (1:1, 1:2 and 1:3 w/w ratio) was kneaded in a glass

mortar with the help of a minimum amount of acetone for 15-20 min and the formed thick paste was dried in the oven (Spectra Equipments, Hyderabad) for 24 h at  $45\pm 1^\circ\text{C}$ . The dried mass was triturated and passed through the sieve no.50 and stored in a desiccator for further evaluations.<sup>21</sup>

### Solvent evaporation method

The solvent evaporation method was employed for the solid dispersion preparation. The carrier SOP and the drug was accurately weighed (1:1, 1:2 and 1:3 w/w ratio) using a digital weighing balance (Electronic balance, AUX 120, Shimadzu, Japan), this physical mixture was solubilized in a minimum amount of acetone till the mixture dissolved completely. Then the solvent was subjected to evaporation using a rotary vacuum flash evaporator (Jain scientific glassworks, India) at temperature  $60^\circ\text{C}$  until the dried mass was obtained. This solid residue was pulverized using a porcelain mortar and pestle. The pulverized powder was passed through sieve no.50 and stored in a desiccator for further studies.<sup>22</sup>

### Saturation solubility study

The glass vials were filled with 5 mL of the dissolution media (0.1 N HCl+0.5% Myrj 52) and an excess of the ART SD was added to it. The solution was then kept for shaking for 48 h in a thermostatic water bath at a temperature of  $37\pm 0.5^\circ\text{C}$ . The sample solution was removed after 48 h, filtered using membrane filter, diluted suitably and analyzed by UV spectrophotometry at  $\lambda_{\text{max}}$  of 210 nm.<sup>23</sup>

### Solid-State Characterization

#### FTIR study

The FTIR analysis was carried out using an FTIR spectrophotometer (Model- IR Affinity 1S, Shimadzu, Japan). The plain ART, SOP, physical mixture of ART and SOP (PM), and optimized SD system were scanned separately for obtaining the spectra. The samples were triturated with KBr then kept in the sample cell and scanned in the range from 4000 to  $800\text{ cm}^{-1}$ .<sup>13</sup>

#### DSC studies

The DSC analysis was performed by using Shimadzu DSC 60 PLUS, Japan. The thermal data obtained were processed using TA60 software. The pure ART, SOP, and optimized SD system were studied. 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 ( $50\text{ mL}/\text{min}$ ).<sup>24</sup>

### XRD study

The crystalline nature of ART, PM and optimized SD were evaluated using X-ray powder diffraction studies. The diffraction patterns were obtained on Bruker AXS D8 Advance (Germany) using radiation from Cu  $K\alpha$  with a voltage and current of 40 kV and 35 mA respectively with a scanning rate of  $2^\circ$  per min having angle  $2\theta$  range of  $5\text{-}60^\circ\text{C}$ . The diffractograms obtained were then analyzed.<sup>24</sup>

### SEM study

The surface morphology of pure ART, PM and optimized SD were studied by using a scanning electron microscope, (ZEISS EVO 18 Germany). Double-sided carbon tape was affixed on aluminum stubs over which samples were sprinkled. These prepared stubs were coated with gold and placed in the vacuum chamber and magnification was adjusted for an excellent quality image.<sup>24</sup>

### Formulation of fast disintegrating tablet using optimized solid dispersion

Direct compression method was employed for the tablet batches (AFT1 and AFT2) having optimized solid dispersion with excipients; Ludiflash and Ludipress. The two excipients are ready to use excipients having wide applicability. The manual filling of powder mixture (having 80 mg of SD ~20 mg of ART) into the die cavity was done. Single punch tablet machine (Chamunda Pharma machinery Pvt. Ltd., India) was used with flat-faced 8 mm punches for the compression of tablets at the suitable compression pressure to obtain the hardness close to  $4\pm 0.5\text{ kg}$ .<sup>19</sup>

### Evaluation of tablets

#### Weight variation

The tablet from the two batches was taken ( $n=10$ ), weighed individually and the average weight was calculated. The % weight variation was evaluated by the equation given below:

$$\text{Weight variation (\%)} = \frac{\text{Individual tablet weight} - \text{Average tablet weight}}{\text{Average tablet weight}} \times 100$$

#### Thickness and diameter

The thickness and diameter of the tablet(s) ( $n=10$ ) from each batch were obtained using a vernier caliper (Veego Scientific, India) and the mean value was then calculated.

### Friability

The previously weighed tablets from two batches ( $n=6$ ) were placed in the friability chamber (Veego Scientific, India) and subjected for rotation at 25 rpm for 4 min. Then the tablets were removed and again weighed. The friability was taken as the percent of the weight loss during the rotation and was calculated by the equation given below:

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

### Drug content

The UV method was developed for drug content estimation with methanol having equation  $y=0.0067x+0.0477$  with  $R^2=0.9973$  (20-100  $\mu\text{g/mL}$ ). A tablet was transferred to a 50 mL volumetric flask containing 10 mL of methanol and was diluted to 50 mL with the same solvent and sonicated (PCi, India) for 30 min. The solution was filtered through a membrane filter and the filtrate was diluted suitably and analyzed by UV spectrophotometry at  $\lambda_{\text{max}}$  of 210 nm.

### In-vitro disintegration time

The USP Disintegration apparatus (Campell Electronics, India) was used for the disintegration test. The tablets ( $n=6$ ) from each batch were placed in the disintegrator cells previously filled with 0.1 N HCl equilibrated at  $37\pm 0.5^\circ\text{C}$ . The sinker was placed after placing the tablet and the time was recorded till the tablet fragments passed through the sinker screen. This point was taken as the disintegration time (in sec).<sup>25</sup>

### Screening of antimalarial activity

The culture of *Plasmodium falciparum* of Chloroquine sensitive (3D7) strain was used for the *in-vitro* antimalarial activity. The samples (plain drug ART and the ART SD) were tested against *P. falciparum* 3D7. RPNI medium supplemented with 25mM HEPES, 0.2% D-glucose, 0.21% sodium bicarbonate, and 0.5% ALBUMAX-II was used for the routine maintenance of the culture. The tested sample stock solutions were prepared using DMSO (5.0 mM) and required dilution was added to the culture medium. Malaria SYBR Green I-based fluorescence (MSF) assay was employed for the estimation of the 50% Inhibitory concentration ( $\text{IC}_{50}$ ) for the samples.

### Assay technique

The highest concentration of 5.0  $\mu\text{M}$  was used for the test compounds. Suitable dilutions were added in 96 well-plate and incubated with 1.0% parasitized cell

suspension with 0.8% parasitemia (Asynchronous culture with > 80% ring stage). The incubation of the well-plate was carried out at a temperature of  $37^\circ\text{C}$  in an atmosphere of a mixture of 5%  $\text{CO}_2$  and air for 72 h. After the time duration of incubation, lysis buffer (100 $\mu\text{L}$ ) containing SYBR Green-I was added to the plate and further incubated for 1h at  $37^\circ\text{C}$ . Then each well was inspected at  $485\pm 20$  nm for excitation and  $530\pm 20$  nm for emission in relative fluorescence units (RFUs) by using a fluorescence plate reader (FLX800, BIOTEK). The  $\text{IC}_{50}$  values were obtained by dose-response curves by employing Logit regression analysis. The reference drug used was Chloroquine diphosphate.

### In-vitro cytotoxic activity

Monkey kidney fibroblast cells (C1008; Vero cell line) were used for the *in-vitro* cytotoxicity activity of test samples (Plain ART and optimized SD). The Vero cells were incubated with samples (after suitable dilutions) for 72 h and MTT reagent was used for the estimation of the cytotoxic activity. The highest concentration (200 $\mu\text{M}$ ) was utilized for the test samples. The 50% cytotoxic concentration ( $\text{CC}_{50}$ ) was determined using dose-response curves. Podophyllotoxin was used as the reference drug. Selectivity Index (SI) was calculated by using the formula as given below with selection criteria  $\text{SI} > 50$ .<sup>26,27</sup>

$$\text{SI} = \frac{\text{CC}_{50}}{\text{IC}_{50}}$$

### In-vitro dissolution study

The dissolution studies were accomplished to ensure the quick release of the drug in the dissolution medium using the USP type I dissolution apparatus (Electrolab, India) at a speed of 100 rpm. The ART SD was compared with the plain ART, marketed tablet, AFT1 and AFT2. The *in-vitro* dissolution was performed in 0.1 N HCl + 0.5 % Myrj 52. Sample aliquots of 5 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 UV spectrophotometry at 210 nm and the percent drug release at each dissolution time point was calculated. For each sample, the test was performed thrice and the results were presented as mean  $\pm$  S.D. The graph was plotted as % cumulative drug release versus time.

### Accelerated stability study

The optimized tablet AFT2 was added inside the capped glass vial wrapped with aluminum foil and placed in

the humidity chamber (REMI Electrotechnik Ltd., Vasai, India) at a temperature of  $40 \pm 2^\circ\text{C}$  and humidity condition at  $75 \pm 5\%$  RH and room temperature. After 3 months of duration, the samples were removed and evaluated for the drug content and % cumulative drug release.

### Pharmacokinetic study

#### Animals

Male Swiss albino mice (weight 30-35 g) were housed in polypropylene cages at a temperature of  $25 \pm 2^\circ\text{C}$  with a relative humidity of  $55 \pm 5\%$ , having free access to diet and water. Before experimentation, the animals were fasted for 8 h with free access to water. The protocol was approved by the Institutional Animal Ethics Committee (IACE/UDPS/2017/17) and was strictly followed as per the guidelines of the committee.

#### Administration of dosage form and collection of blood samples

Animals were divided into two groups of four animals per group ( $n=4$ ). ART SD tablet suspension was administered to Group 1 animals while Lumerax DT (Ipca, India) tablet suspension was administered to Group 2. All the suspensions were equivalent to ART (1 mg/kg body weight) diluted with 0.5% sodium alginate solution administered orally once to both the groups. The plasma samples were collected at time intervals of 0.25, 0.5, 1, 2, 6, 12, 24, 48, 72 h after administration. The sample of blood (0.25 mL) was taken from the retro-orbital plexus of the mice into the heparinized tubes. The tubes with the blood were centrifuged at 10,000 rpm for 10 min to extract the plasma and stored at  $-20^\circ\text{C}$  for further analysis.<sup>28</sup>

#### HPLC method for drug analysis

Before the quantification of ART in plasma samples, the calibration curve of plain ART was constructed in the plasma (ART free). The plasma sample (100  $\mu\text{L}$ ) was mixed with 50  $\mu\text{L}$  of internal standard solution (Artesunate 100  $\mu\text{g}/\text{mL}$ ) and 50  $\mu\text{L}$  of drug solution (methanol containing ART) and vortexed (Impact, Icon Instruments Company, Delhi) for 30s then protein precipitating agent acetonitrile (500  $\mu\text{L}$ ) was added and vortexed for 1 min. The mixture was centrifuged for 20 min at 10,000 rpm and the supernatant was filtered and 20  $\mu\text{L}$  of the filtrate was injected into the HPLC system.<sup>28,29</sup> The mobile phase consisted of acetonitrile: methanol (50:50 v/v) and 0.01 M ammonium acetate (pH 4.5) in the ratio of 95:5 (v/v). The system was run in an isocratic mode having 1 mL/min of flow rate. The sample was injected with a volume of 20  $\mu\text{L}$  and

monitored at a wavelength of 216 nm with a runtime of 2.019 min for ART. The reconstituted standard solution was applied to the HPLC and chromatograms were obtained. The calibration curve was plotted as peak area ratio versus drug concentration for quantification of ART in the plasma. The calibration graph was linear in the range of 3.4-14.3  $\mu\text{g}/\text{mL}$  ( $y=0.0078x-0.029$  with  $R^2=0.999$ ) for ART. The sample plasma obtained after administration of ART formulations under the investigation was spiked with the internal standard solution and the same procedure was applied as performed for the standard sample. This slight modified HPLC method was found to be easy, precise and suitable for the routine analysis of ART in plasma.

#### Analysis of data for pharmacokinetic study

The pharmacokinetic data obtained from the study was processed using PK Solver software. The various evaluation parameters ( $C_{\text{max}}$ ,  $T_{\text{max}}$  and  $\text{AUC}_{0-24}$ ) were evaluated from the plasma concentration-time curve by using non-compartmental analysis. The ratio of the  $\text{AUC}_{0-\infty}$  of the optimized tablet to that of the  $\text{AUC}_{0-\infty}$  of the marketed tablet known as relative bioavailability was also calculated.

#### Statistical analysis

The experiment was carried out thrice and the results were represented as mean  $\pm$  S.D.

## RESULTS AND DISCUSSION

### Phase solubility study

The prerequisite for the formulation of the solid dispersion is the selection of the hydrophilic carrier which will increase the aqueous solubility of hydrophobic ART. To ascertain this task, the carrier such as Kollidon VA64, Plasdone S630 and Soluplus were chosen on the basis of earlier literature on solid dispersion.<sup>1,12,24</sup> The solubility of ART in the presence of the hydrophilic carriers played a key role in the final selection. Thus, the study helped to gain an insight on the influence of the hydrophilic carriers with different concentrations on the drug solubility. Figure 1 represented ART solubility in the aqueous solutions of hydrophilic carriers in various concentrations (1-10% w/v). The experimentally calculated solubility of ART was found to be 0.0017  $\mu\text{g}/\text{mL}$  which was concordant with the previous literature.<sup>23</sup> The ART solubility increased with the increasing concentration of the hydrophilic carriers and after a certain point, there was no further increase in the solubility. The highest solubility was observed for SOP in comparison with the other carriers. The

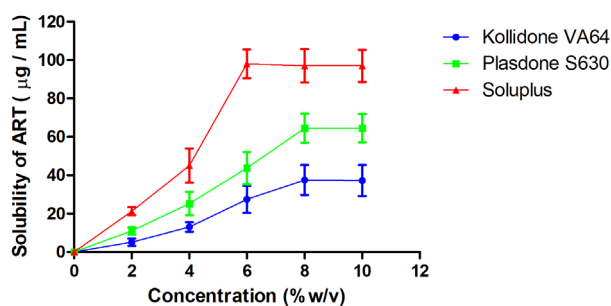


Figure 1: Phase solubility study.

maximum solubility achieved was 93.23 µg/mL in the SOP solution at a concentration of 6% w/v. This suggested the higher affinity of SOP for the ART and vice versa which could favor the formation of the dispersion at the molecular level. The SOP (polyethylene glycol-polyvinyl caprolactam acetate grafted copolymer) consists of both lipophilic and hydrophilic moiety. Thus, the amphiphilic nature of SOP leads to higher solubilization of the drug in the aqueous solution. The SOP is nowadays frequently utilized for various poorly water-soluble drugs.<sup>13,25</sup> The mechanism by which the drug solubility is improved lies in the ability of the SOP to form micelles in the aqueous solution resulting in the higher dissolution. Due to the presence of a large number of electron-withdrawing groups (mainly O atoms), it was suggested for the higher possibility for the formation of hydrogen bonds between the drug and the SOP.

### Selection of method of preparation of solid dispersion

Based on the phase solubility results, the best hydrophilic carrier nominated was SOP for the final formulation of the solid dispersion of ART. The two methods for the preparation of the solid dispersion such as kneading and solvent evaporation were chosen and the effect of the micellization upon increasing the ratio of the SOP (ART: SOP; 1:1, 1:2 and 1:3) was studied. The kneading method is reported to be very stable and much more convenient for the formulation of the oral dosage form such as tablet.<sup>30,31</sup> This method is non-hazardous to the environment and also cost-effective.<sup>21</sup> The solvent evaporation method by using a rotary evaporator leads to the evaporation of the acetone (solvent) in a controlled manner that leads to uniform mixing of the ART and the hydrophilic carrier. This is a simple and single-step process in which the parameters of evaporation (temperature and rpm) can be controlled quite easily. This method is thus not very complex. Thus, conversion of the drug from crystalline state to amorphous

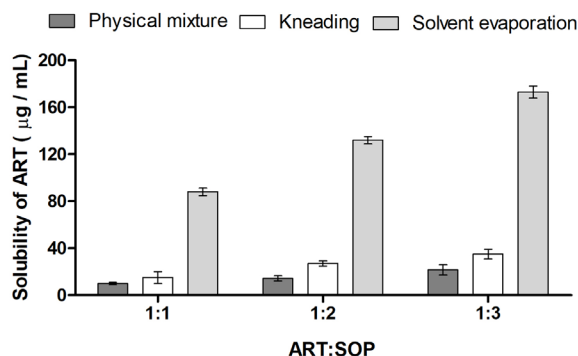


Figure 2: Solubility study of physical mixture of ART and solid dispersion prepared by kneading and solvent evaporation.

state could be expected. The solvent evaporation by rotary evaporator was opted as it prevented ART degradation, caused no threat to the environment with cost-effective benefit. After the consideration of all the above advantages, the rotary evaporation method was thus opted. The evaporation of the solvent was carried out under reduced pressure and high temperature.<sup>13</sup> The concentration of the hydrophilic carrier that affected the ART solubility is depicted in Figure 2. The SD improved the solubility of ART significantly than observed for the corresponding physical mixture. The higher improvement in the solubility was achieved with the SD obtained from the solvent evaporation method than the kneading method. As the ratio of the hydrophilic carrier was increased, there was an increase in the solubility of the ART. The SOP underwent the micellization process that favors higher solubilization of the ART in the aqueous solution. Higher the micelle formation higher the drug solubility observed when the ratio of SOP was increased in the respective solid dispersions.<sup>11</sup>

### Saturation solubility study

The solubility study was carried out by employing three ratios of physical mixture and prepared SDs (ART: SOL in 1:1, 1:2, 1:3 w/w). The different methods selected were kneading and solvent evaporation for the preparation of the SDs. The physical mixture showed solubility of 9.97±1.0 µg/mL, 14.32±2.2 µg/mL and 21.56±4.3 µg/mL respectively. The SDs prepared by kneading method had solubility of 15±5.1 µg/mL, 27±2.2 µg/mL and 35±4.1 µg/mL respectively. The solubility of SDs prepared using solvent evaporation method was 88±3.3 µg/mL, 132±3.1 µg/mL and 173±5.1 µg/mL respectively. The study revealed the increased solubility of ART from the prepared SDs. Both the methods were able to improve the solubility of drug. The higher solubility

was obtained from the solvent evaporation method as compared to the solubility of the SDs prepared by kneading method. The reason could be effective mixing of the drug and SOP under high temperature and pressure that allowed maximum interaction. In the kneading method, there is only mixing using the solvent without heat application. Thus, the kinetic motion of the molecules of ART and SOP that sets out during heating allowed homogenous fusion which was absent in the kneading method. Hence, solvent evaporation method was finalized for the preparation of SDs and the ratio of 1:3 was chosen due to higher solubility value.

### Characterization of solid dispersion

#### FTIR study

FTIR spectra of the characteristic peaks of ART, SOP, PM (ART+SOP) and SD of the optimized batch were studied as shown in Figure 3. FTIR spectrum of ART presented characteristic peak at OH stretch at 2951.09  $\text{cm}^{-1}$ . The C-H stretching was observed at 2843.07  $\text{cm}^{-1}$ , C-H bending at 1373.32  $\text{cm}^{-1}$ , C-O-C stretching at 1136.07  $\text{cm}^{-1}$  and C-O-O-C bending at 1188.15  $\text{cm}^{-1}$ . The H-C=O stretching at 2721.56  $\text{cm}^{-1}$ ,

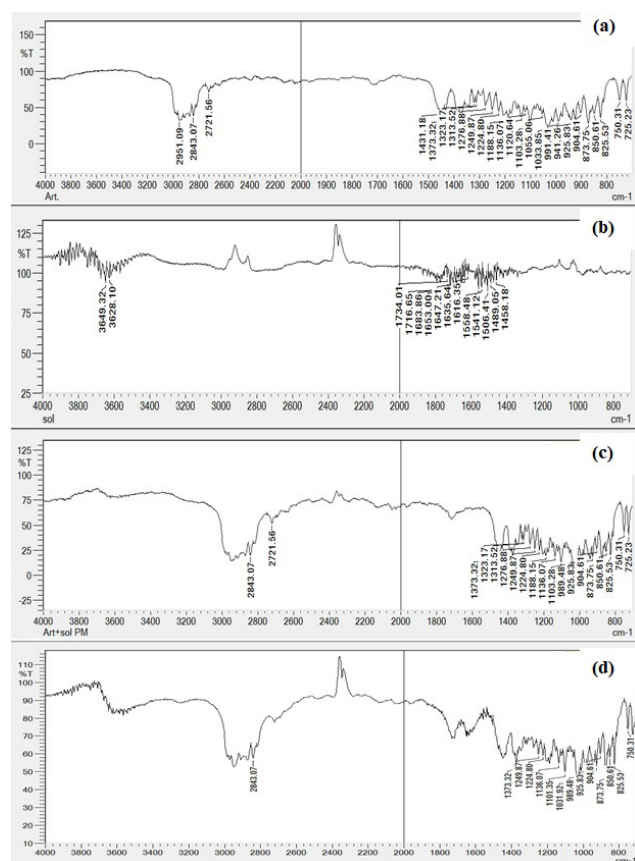


Figure 3: FTIR spectra of (a) ART, (b) SOP, (c) Physical mixture (ART+SOP) and (d) A3 SD.

aromatic C-H at 1431.18  $\text{cm}^{-1}$ , -C-H at 1373.32  $\text{cm}^{-1}$ , alcohol C-O stretching at 1055.06  $\text{cm}^{-1}$ , ether C-O stretching at 1033.85-1276.88  $\text{cm}^{-1}$ . The FTIR spectra of SOP exhibited various peaks for C=H aromatic stretching at 1489.05  $\text{cm}^{-1}$ , C=O stretching at 1734.01  $\text{cm}^{-1}$  and the free OH stretching at 3649.32  $\text{cm}^{-1}$ . The peaks observed for ART and SOP were concordant with the previous findings.<sup>27</sup> The spectra of ART+SOP and optimized SD A3 were found to be nearly similar suggesting no incompatibility occurred in the PM as well as in the SD formulation. The characteristic OH stretching peak at 2951.09  $\text{cm}^{-1}$  and H-C=O stretching at 2721.56  $\text{cm}^{-1}$  were disappeared in the FTIR spectra of A3 as a result of interaction because the hydrogen bonding operated between ART and SOP. The interaction was observed in the PM and SD system. This interaction between the ART and SOP exhibited formation of molecular dispersion and thus were not affected chemically which means that both the components of the SD system were compatible.

#### DSC study

The DSC thermograms of SOP, ART and ART SD A3 were studied which are represented in Figure 4. No endotherm of SOP was observed because of its amorphous nature. Pure ART showed a sharp endothermic peak at 86.52 °C with an enthalpy change of 44.01 J/g and an exothermic peak at 163.59 °C with

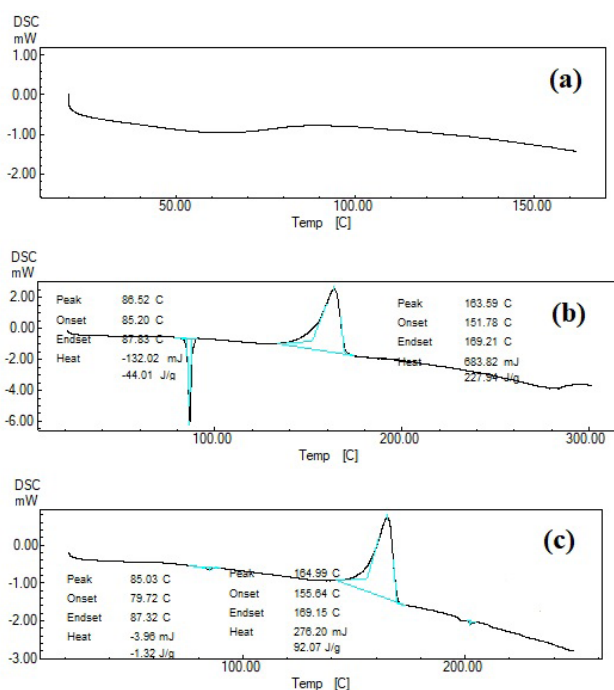


Figure 4: DSC thermogram of (a) SOP, (b) plain ART, and (c) A3 SD.

an enthalpy of 227.94 J/g. These results suggested that ART was crystalline and was in line with the previous literature.<sup>23</sup> In the A3 SD system, the disappearance of the characteristic sharp endothermic peak of ART was observed with melting event of ART at a temperature of 85.03°C with enthalpy of 1.32 J/g. The exothermic peak was observed at a temperature of 164.99°C having an enthalpy of 92.07 J/g. The drop in the enthalpy of the endothermic (from 44.01 J/g to 1.32 J/g) and exothermic peaks (from 227.94 J/g to 92.07 J/g) of ART suggested that there may be some degree of interaction between ART and SOP in the SD. The thermogram of the SD A3 suggested the formation of solid dispersion with conversion into the amorphous form. These results also suggested reduction in the crystallinity of ART that contributed to the increased drug solubility. Interactions such as hydrogen bonding may be the

possible reason. These results are in agreement with the FTIR studies.

### XRD study

The X-ray diffractograms of ART, PM and optimized SD are shown in Figure 5, which illustrates the vital modification in the structure of ART crystal after the SD formation. From the XRD diffraction pattern of pure ART, it was suggested that it is a crystalline compound, showing a very strong diffraction peak at  $2\theta$  of  $9.653^\circ$  with intensity count = 547410 Lin (Counts) and other peaks at  $2\theta$  of  $10.300^\circ$ ,  $11.404^\circ$ ,  $19.395^\circ$ . PM represented the weak diffraction peak intensity count = 6500 Lin (Counts) with the peak at  $2\theta$  of  $9.979^\circ$ . In the case of ART SD (1:3) diffraction peak was at  $2\theta$  of  $9.939^\circ$  with intensity count = 3500 Lin (Counts) can be seen in the diffractogram. The diffractogram of A3 SD depicted low peak intensity with decreased crystallinity. Thus, A3 SD prevented crystallization tendency and kept the dispersion at the molecular level into the matrix of the hydrophilic carrier. The crystalline status of ART changed because of SOP, with most characteristic ART peaks appeared diminished suggested that ART was converted into the amorphous form. The loss of ART crystalline structure occurred due to the interaction between the drug and SOP. It was also confirmed from the A3 diffractogram that ART was uniformly and completely dispersed into the hydrophilic matrix carrier. This data also corresponds with the DSC studies.

### SEM study

SEM photomicrographs of free ART, PM and optimized SD were used for the morphological study. SEM

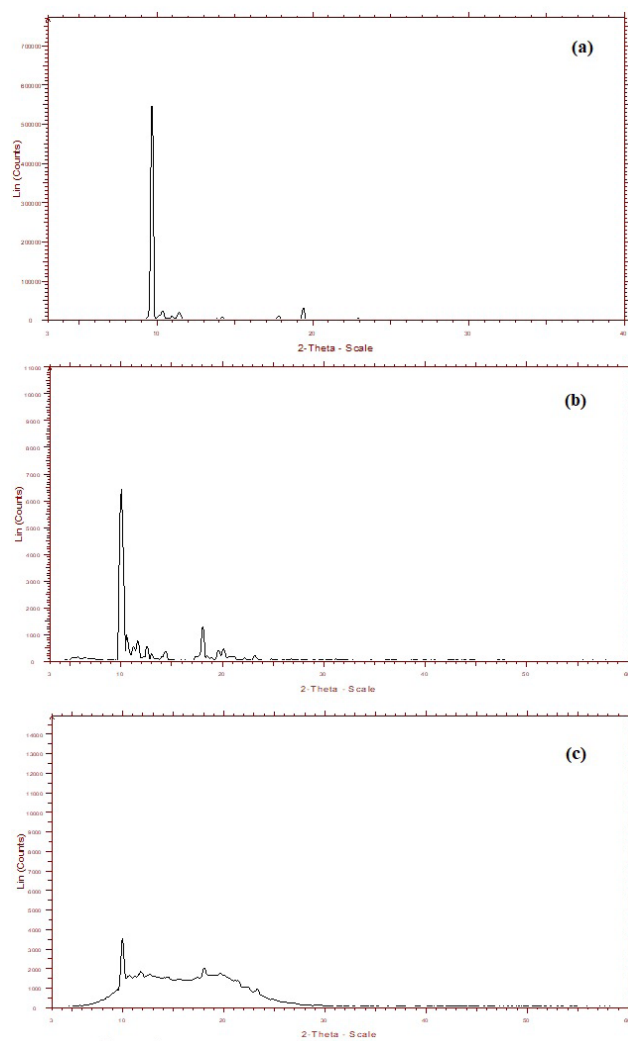


Figure 5: XRD of (a) ART, (b) physical mixture (ART+SOP) and (c) A3 SD.

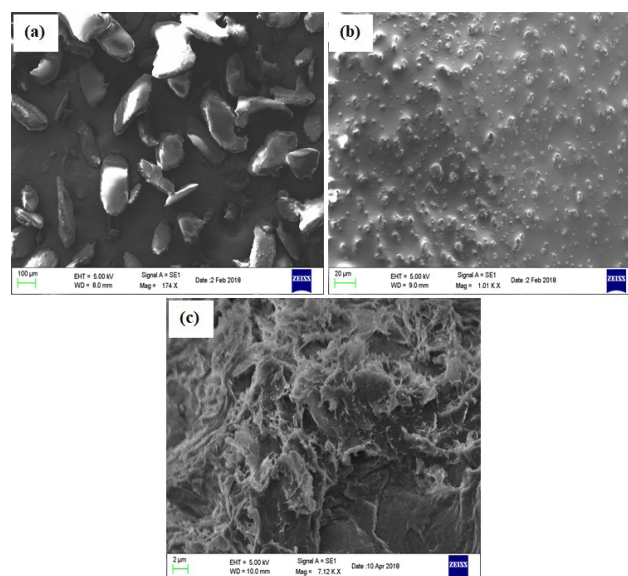


Figure 6: SEM images of (a) ART, (b) physical mixture (ART+ SOP) and (c) ART SD.



photographs of ART alone showed typical large crystalline blocks having sharp edges and non-uniform particle shapes as shown in Figure 6. SOP showed irregular-shaped spherical particles with rough surfaces in the physical mixture. The prism-shaped ART crystals were absent and thus were different from the pristine drug depicting the formation of the SD A3. The SD A3 appeared to be agglomerated and the fusion of components was observed. The ART and SOP structures were lost during the rotary evaporation. The reason may be that the drug was completely fused with SOP. This inhibited the recrystallization of ART in solid dispersion. Deposition of the ART was observed on SOP in the case of the SD A3. The ART presented amorphous nature having close contact with the hydrophilic carrier and which is critical in enhancing drug solubility and dissolution rate.

### Screening of antimalarial activity

*In-vitro* antimalarial activity demonstrated a small concentration of SD A3 showed activity against *P. falciparum* 3D7 having  $IC_{50}$  of 0.059 ng/mL while for the plain ART, the value was 0.24 ng/mL. Thus it was concluded that SD A3 represented higher activity against malarial parasite than the corresponding plain ART as well as the standard antimalarial drug, Chloroquine ( $IC_{50}$  value of 1.73 ng/mL). The formulation of SD with the SOL improved the solubility that aided in the enhanced antimalarial activity and inhibited the parasite. It can thus be concluded that the prepared SD A3 showed higher antimalarial efficacy as compared to plain drug ART and standard drug.

### *In-vitro* cytotoxicity assay

The *in-vitro* cytotoxicity study was carried out to check whether the SD would harm the healthy cells of the body or remain neutral. Hence, the Vero cell line was chosen as this cell line is routinely used to carry out the toxicity study. The  $CC_{50}$  value of ART SD was found to be 397.79  $\mu$ g/mL as compared to ART (520  $\mu$ g/mL). Cytotoxic activity on Vero cell lines showed a selectivity index of >50 for A5 indicating its non-toxicity. It was

observed that ART SD showed no toxicity in monkey kidney cells.

### Formulation of fast disintegrating tablet using optimized solid dispersion

The direct compression method for tablet production is one of the widely applied and convenient methods.<sup>32-34</sup> The process of compression using a directly compressible excipient is quite easy and cost-effective for the industrial application with a minimum number of steps involved in it. The tablet formulations are sturdy because special packaging is not required with ease in modulation for handling. The mechanical characteristics of the tablet such as friability, hardness and disintegration are not affected much and can withstand the external stress in a better fashion.<sup>34,35</sup> The important aspect that is needed to consider is the right selection of the excipients for the tablet as it can affect the physicochemical characteristics of the final tablet formulation. Thus, tablets were prepared by direct compression (200 mg weight of each tablet) of the selected solid dispersion A3. The investigation was made by studying the effect of two tablet excipients; Ludiflash and Ludipress on the tablet properties. Ludiflash is mainly co-processed mannitol (90%) with crospovidone and polyvinyl acetate. The characteristic features of Ludiflash are good flowability, taste-masking properties and good compressibility that results in short disintegration time and consequently faster dissolution rate with enhanced palatability with smooth mouth feeling.<sup>36</sup> Ludipress is free-flowing, white powder of Lactose monohydrate (93%) with povidone and crospovidone. The characteristic properties are high flowability with excellent blending capacity.<sup>37</sup>

### Evaluation of ART SD fast disintegrating tablets

Tablets were successfully prepared by direct compression using Ludiflash and Ludipress. Table 1 presents the composition and evaluation parameters of the prepared tablets. The tablets had satisfactory organoleptic properties such as pearl white appearance, compact structure and durability for ease in handling.

**Table 1: Characteristics of the prepared tablets.**

Tablet code	Excipient	Mean Diameter (cm)	Mean Thickness (cm)	Weight variation (%)	Drug content (%)	Friability (%)	Disintegration time (s)
AFT1	Ludiflash	0.82±0.05	0.252±0.008	0.31±0.005	98.12±0.38	0.216±0.08	93±12
AFT2	Ludipress	0.83±0.04	0.253±0.007	0.47±0.006	97.93±0.71	0.241±0.06	289±35

Regarding physical properties, it was observed that there was uniformity in the diameter and thickness of the tablets with very less values of weight variation. The tablets had higher ART content (>90 %) as obtained in the drug content assay. In the friability test, the tablet batches under the study were compact without the occurrence of any cracking or capping and less than 1% weight loss was observed (0.321-0.448) which was in line with the reported pharmacopoeial limits.<sup>34</sup> The AFT1 tablets gave a short disintegration time (< 2 min) compared to the AFT2 tablets (> 4 min). The reason could be higher porosity and quick penetration of water deep into the tablet due to the presence of mannitol in Ludiflash with no blocking of the pores and quick action of the disintegrant.

### In-vitro dissolution study

The dissolution study was executed for the ART, marketed tablet, A3 and the prepared tablets (AFT1 and AFT2) as shown in Figure 7. The drug release from A3 was 98.25% and plain ART showed only 57.46% release at the end of 2 h which suggested the slower rate of dissolution due to poor aqueous solubility while the SD A3 and the tablets (AFT1 and AFT2) showed improved dissolution rate. The enhanced solubility of ART was observed as a result of the formulation of the solid dispersion employing the hydrophilic carrier i.e., SOP. In the dissolution process of the tablets, SOP played a

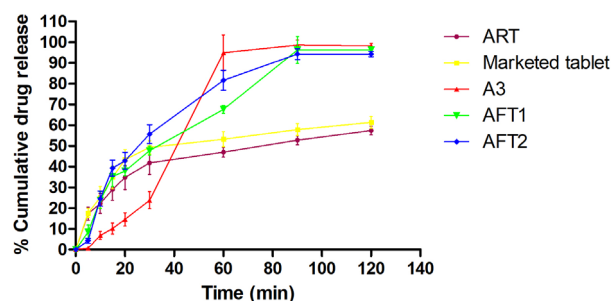


Figure 7: Cumulative drug release of drug.

vital role in quickly solubilizing the ART and ensured that a larger volume of the dissolution medium was swapped by the ART. This was possible due to the wetting of ART in the presence of the SOP. During the formation of the SD, the hydrophilic matrix of SOP entraps the ART which leads to the overall coating of the ART uniformly. The ART is crystalline and when the heating and evaporation occurs, there is a breaking of the crystalline lattice of the ART structure forming a disordered random structure imparting amorphous form. Thus, the particle size of the drug gets reduced which provides a larger surface area for the interaction with the dissolution media leading to the higher solubilization followed by dissolution.<sup>23-25</sup> The transition from the crystalline state to the amorphous state of ART due to the solid dispersion formulation as confirmed from DSC and XRD studies resulted in enhanced dissolution rate due to decreased surface tension between the drug and dissolution media brought about by SOP through the micellar solubilization. The comparison between the AFT1 and AFT2 tablets was performed which showed higher dissolution from AFT1 tablets. The drug release from AFT1 and AFT2 tablets after 2 h was 96.21% and 94.26% respectively. The SD A3 and the tablets were superior in the dissolution rate from the marketed tablet as well as plain ART. The AFT1 and the SD A3 shared an almost similar pattern of dissolution profile. The release kinetic data is presented in Table 2. It was concluded that the plain ART fitted into Higuchi modeling, the SD A3 followed Korsmeyer-Peppas release with  $n$  value >1 with non-fickian release super case 2 while the marketed tablet also depicted Korsmeyer-Peppas release with  $n$  value <0.45 with quasi diffusion mechanism. The AFT1 and AFT2 tablets showed the Higuchi release mechanism.

### Accelerated stability study

No significant change in drug content and *in-vitro* release study was observed in the accelerated stability study as shown in Table 3 and the tablets were stable at

Table 2: In-vitro release kinetic modeling for various formulation of ART.

Formulation	Zero order plot	First order plot	Higuchi plot	Korsmeyer-Peppas plot	
				R <sup>2</sup>	n
Plain ART	0.7546	0.9076	<b>0.9695</b>	0.9615	0.3763
SD A3	0.8599	0.8654	0.8993	<b>0.9348</b>	1.462
Marketed tablet	0.6698	0.8167	0.8579	<b>0.8969</b>	0.3757
AFT1	0.914	0.8654	<b>0.9657</b>	0.9458	0.694
AFT2	0.8443	0.8654	<b>0.9438</b>	0.8364	0.7823

**Table 3: Stability study of tablet AFT1.**

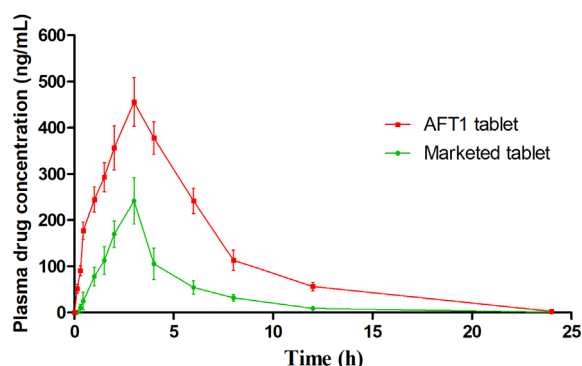
Evaluation parameter	0 day at room temperature	3 months at room temperature	3 months at 40 °C 75% RH
<i>In-vitro</i> dissolution study	91.26±2.1%	90.98±1.9%	90.96±2.3%
Drug content %	99.12±2.25%	98.95±2.11%	98.92±1.36%

Each value represented the mean ± S.D. (n=3)

**Table 4: Pharmacokinetic parameters for different formulations.**

Parameters	Marketed tablet	AFT1
$C_{max}$ (ng/mL)	241.87±42	455.82±67
$T_{max}$ (h)	3.205±0.57	2.9248±0.19
$AUC_{0-24}$ (h.ng/mL)	921.751±115	2942.792±553
Relative bioavailability		3.188

Each value represented the mean ± S.D. (n=3)



**Figure 8: Pharmacokinetic profile of prepared tablet and marketed tablet after oral administration.**

both temperatures. Thus, it can be concluded that the SD-based tablets were quite sturdy and can withstand increased temperature also.

### Pharmacokinetic study

The *in-vivo* study using mice was undertaken to evaluate the parameters such as  $AUC_{0-24}$ ,  $C_{max}$  (observed maximum plasma concentration following drug administration) and  $T_{max}$  obtained after oral delivery by plotting the plasma-concentration time profile curve. The plasma concentration versus time graph is depicted in Figure 8. The parameters for the pharmacokinetic study are listed in Table 4. The ART SD tablet represented a significant increase in plasma concentration than the marketed tablet. The  $AUC_{0-24}$  and  $C_{max}$  values of the ART SD tablet were 1.88 times and 3.19 times higher than the marketed tablet respectively. The improved bioavailability can be

due to the formation of solid dispersion of ART, as a result, the high plasma level of the drug was achieved quite faster. A slight decrease in the  $t_{1/2}$  of ART SD tablet was observed. The reason could be the higher and quick dissolution of ART which resulted in spiking drug loading into the systemic circulation. Thus the pharmacokinetic studies showed an improvement in the bioavailability of the drug.

### CONCLUSION

The present work aims to formulate a quick disintegrating tablet of Artemether for the efficient therapy of malaria. The solid dispersion was prepared using Soluplus to improve the solubility of the Artemether by the solvent evaporation method. The A3 (ART: SOP ratio 1:3) showed maximum solubility and also had higher antimalarial efficacy as compared to the plain drug. The optimized solid dispersion was formulated into the fast disintegrating tablet and *in-vitro* dissolution study exhibited rapid dissolution of the drug. *In-vivo* pharmacokinetic studies in mice showed significant improvement in bioavailability of the ART. Thus, Artemether solid dispersion in the fast disintegrating tablet may prove to be a promising approach in the effective treatment of malaria.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### ABBREVIATIONS

**ART:** Artemether; **SOP:** Soluplus; **PM:** Physical mixture; **MAR:** Marketed tablet; **SD:** Solid dispersion; **DSC:** Differential scanning calorimetry; **FTIR:** Fourier transformed infrared spectroscopy; **HPLC:** High-performance liquid chromatography; **SEM:** Scanning electron microscopy; **XRD:** X-ray diffraction; **DMSO:** Dimethyl sulphoxide.

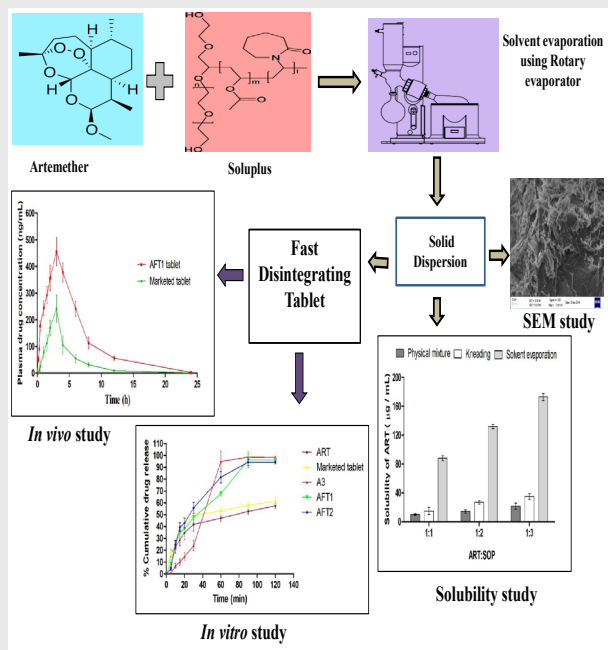
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## PICTORIAL ABSTRACT



## SUMMARY

The Artemether is having poor aqueous solubility and is frequently used in the treatment of malarial therapy. Solid dispersion was formulated using Soluplus by rotary evaporation technique and then the formed solid dispersion was incorporated in a suitable dosage form such as a fast disintegrating tablet. The characterization of the solid dispersion was performed using FTIR, DSC, XRD and SEM which showed conversion from crystalline to an amorphous form of Artemether. The phase solubility study showed higher efficacy with Soluplus. Thus, solid dispersion of the drug was prepared using Soluplus. The different ratios were tried and saturation solubility study was performed for all three ratios which revealed that the 1:3 ratio had higher aqueous solubility. The dissolution studies showed an improved dissolution rate with more than 90% of drug release. The *in-vitro* antimalarial screening was performed using *Plasmodium falciparum* 3D7 cell line assay which showed increased efficacy of the formulated solid dispersion. The *in vitro* cytotoxicity study was carried out using Vero cell line which depicted the safety of the formulated solid dispersion. The *in-vivo* pharmacokinetic study showed increased bioavailability of the Artemether when formulated in solid dispersion.

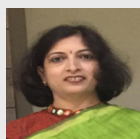
## About Authors



**Pranita S. Kanojiya:** She is a Ph.D. research scholar at the Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur.



**Yogita M. Charde:** She is currently working as an Assistant Professor at Sai Nath College of Pharmacy, Nagpur.



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

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