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Development and Evaluation of Artemether-Aeroperl® 300 Pharma Granular Solid Dispersion Powder with Enhanced Solubility, Dissolution Rate and Physicochemical Characterisation

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ABSTRACT

The objective was to enhance the solubility and dissolution rate of Artemether poorly water soluble antimalarial, by the preparation of solid dispersion (SD) granules. The dispersion granules were prepared using a hot melt granulation technique which involved the preparation of a homogenous dispersion of ARTM in surfactant melt, followed by its adsorption onto the surface of AEROPERL® 300 Pharma, an inert absorbent using the solvent evaporation method. The dispersion granules were characterized for their in-vitro dissolution rate, moisture content and flow properties. The formulation was further characterized by FTIR,DSC, XRD and SEM analysis. FTIR spectrum revealed some drug excipient interactions. DSC and XRD data indicated the retention of amorphous form of ARTM. SEM confirmed the homogeneity and surface adsorption of the ARTM-Lutrol F127 or ARTM-Lutrol F68 melt on AEROPERL® 300 Pharma leading to an enhanced surface area and thus the dissolution rate. The optimized dispersion granules were filled inside the capsules and evaluated. The in-vitro dissolution rate of these capsules was significantly better in comparison with pure drug. Physical characterisation enabled us to understand the effects of formulation variables on the dispersion granules of ARTM.

Keywords: Artemether, AEROPERL® 300 Pharma, Dissolution rate, Solubility, Melt method, Solid dispersion.

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INTRODUCTION

Artemether (ARTM) is a poorly soluble and poorly permeable BCS class IV drug used for prevention of malaria. ARTM is a potent antimalarial agent accessible for the treatment of severe multiresistant malaria and is included in WHO list of essential medicines (WHO web site). It is active against *P. vivax* as well as chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* and is also indicated in the treatment of cerebral malaria. However, the therapeutic potential of ARTM is substantially delayed due to its low oral bioavailability (~40%). The low bioavailability of ARTM shoots from its poor aqueous solubility[1]. The poor water solubility of drug substances and their low rates of dissolution in the aqueous gastrointestinal fluids often lead to insufficient bioavailability, and this remains a problem to the pharmaceutical industry. Solid dispersions of hydrophobic drugs in water-soluble carriers have attracted considerable interest as a means of improving dissolution behaviour, and hence enhancing bioavailability[2,3]. The most commonly used hydrophilic carriers for soliddispersions include polyvinylpyrrolidone[4], polyethyleneglycols[5],colloidal silicon dioxide [6], and lipids, suchas polyglycolized glycerides (gelucire)[7]. The solventevaporation[8], melt adsorption[9], fusion[10], spraydrying[11], spray freezing[12], spray congealing[13], meltextrusion[14] and supercritical fluid precipitation[15], arethe techniques reported for the preparation of solid dispersions.Recently, many workers reported solid dispersions usinggelucires (polyglycolized glycerides) by fusion and solventevaporation techniques [16, 17]. Poloxamers belong to a familyof materials which are synthetic copolymers of ethylene oxide and propylene oxide. Polaxomers are available with arange of properties depending on their hydrophilic lipophilicbalance (HLB). They have a HLB over a range of 12 to 25and melting point between 16°C and 57°C. Lutrol F127 and Lutrol F68hydrophilic carriers which are frequently used for this purpose. The Crystallinity reduction and wetting with hydrophilic lipid were reported as the main mechanisms responsible for increased solubility and dissolution rate. A significant increase in the solubility and dissolution rate of etoricoxib was reported in solid dispersions which could be attributed to improvement of wetting of drug particles and localized solubilization by the lipid carriers [18].Some of the challenges in the processing for dosage form development of such materials are difficulty of pulverization and sifting of the dispersions, which are usually soft and tacky, poor flow and mixing properties of powders thus prepared, poor compressibility, drug-carrier incompatibility, and poor stability of dosage forms [19, 22]. These problems thus limit the commercial applications of solid dispersion technology. Surface adsorption technique was reported in order to overcome the problems

associated with solid dispersions of BAY 12-9566 with TPGS or Lutrol F127 or Lutrol F68 which involves the use of an inert adsorbent i.e. neusilin US-2, for the adsorption of the melt of dispersion on its surface [23]. Here the surface adsorbent technique, significantly enhanced dissolution rate, good flow and compressibility of dispersion granules. This technique additionally overcomes a key limitation of solid dispersions, i.e. decrease in dissolution on storage. Optimization techniques provide both a depth of understanding and an ability to explore and define ranges for formulation and processing factors[24].In the present study, AEROPERL® 300 Pharma was used as a surface adsorbent to formulate dispersion granules of ARTM.AEROPERL® 300 Pharma is an inert amorphous material consisting of colloidal silicon dioxide with a mean particle size of 30 μ, a significant pore volume and uniform spherical shape. It also has good flow and compressibility properties. AEROPERL® 300 Pharma in the solid dispersion can potentially resolve the processing issues associated with solid dispersions. Also, AEROPERL® 300 Pharma is less likely to promote the reversion of the amorphous drug to crystalline state on storage of the solid dispersion due to its amorphous nature[25].The aim of the present study was to improve the solubility and dissolution rate of ARTM by formulating a solid dispersion with AEROPERL® 300 Pharma or AEROPERL® 300 Pharma+ Lutrol F127 or AEROPERL® 300 Pharma+ Lutrol F68. The work was further extended to improve the flow properties of the solid dispersion by a surface adsorbent technique[26, 27]. An appropriate statistical model was arrived at and a significant enhanced dissolution rate and flow properties were exhibited with the optimized dispersion granules.

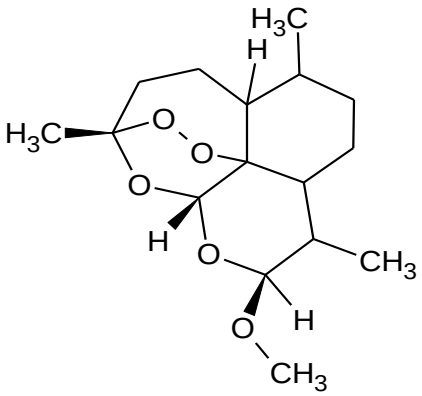


Figure 1 Chemical structure of Artemether

MATERIALS AND METHODS

Materials

ARTM was received from Bajaj Healthcare Pvt. Ltd. Mumbai, India. Aeroperl®300pharmawas obtained from Evonik Corporation, Mumbai, India. Lutrol F127 and Lutrol F68 were gifted from

BASF Pvt. Ltd, Mumbai, India. All the above materials were generously gifted by the respective organizations and were used as received. Solvents and chemicals used were of analytical grade.

Experimental Design

A three-level, two-factor experimental design describes the proportion in which the independent variables Lutrol F127 or Lutrol F68 (X1), and AEROPERL® 300 Pharma (X2), were used in the formulation of dispersion granules[28]. The dissolution rate, as amount dissolved in 10 min (t10), amount dissolved in 30 min (t30) up to 180 min (T180) and compressibility index (CI) were selected as dependent variables. The ratio of quantity of Lutrol F127 or Lutrol F68 to that of drug was constant at three levels, 0.5 and whereas the ratio of quantity of AEROPERL® 300 Pharma to that of drug was varied at the levels of 1, 1.5 and 2.5. All nine formulations were prepared in three sets and analyzed individually for dissolution rate and compressibility index in triplicate. Checkpoint batch was also prepared to prove the identity of the evolved mathematical model. The linear regression model was derived from Enter Method using Design Expert version 8.0.1.7, statistical software. Significance terms were chosen at 95% confidence interval ($p<0.05$) for final equations. In addition, contour and surface plots were obtained to represent the effect of the independent variables graphically.

Table 1 Shows comparative evaluation of ARTM and its SD formulations in terms of aqueous solubility, solubility in dissolution medium [Abbreviation: Artemether- ARTM, AEROPERL®300 Pharma- APL, Lutrol F127- LF127, Lutrol F68- LF68 (mean ± SD (n=3)].

Batch	Formulation Type	Ratio	Processing temp. (°C)	Batch Size(gm.)	Solubility in Water (µg/mL)	Solubility in Disso. Medium (µg/mL)
Drug	Pure ARTM	-	-	-	0.0183±1.3	0.452±1.34
F1	ARTM:APL	1:1	-	4	1.2±1.54	15.69±1.54
F2	ARTM:APL	1:2	-	6	1.23±1.12	21.56±1.08
F3	ARTM:APL	1:3	-	8	1.32±1.69	25.72±1.85
F4	ARTM:SOL:LF127	1:1.5:0.5	65	4	1.6±1.47	35.29±1.15
F5	ARTM:SOL:LF127	1:2.5:0.5	65	6	1.75±1.29	41.52±1.41
F6	ARTM:SOL:LF127	1:3.5:0.5	65	8	1.9±1.36	44.26±1.52
F7	ARTM:SOL:LF68	1:1.5:0.5	70	4	1.3±1.12	20.53±1.71
F8	ARTM:SOL:LF68	1:2.5:0.5	70	6	1.4±1.24	28.92±1.16
F9	ARTM:SOL:LF68	1:3.5:0.5	70	8	1.6±1.56	34.15±1.92

Method of Preparation of Dispersion Granules

Solid dispersion granules of ARTM with AEROPERL® 300 Pharma, Lutrol F127+ AEROPERL® 300 Pharma and Lutrol F68+ AEROPERL® 300 Pharma in the ratios as mentioned in Table 1; were prepared by incorporating ARTM into the melt of Lutrol F127 or

Lutrol F68 at a temperature between 65°-70°C until a homogenous melt was obtained. This melt was cooled, powdered and 20 ml of analytical grade acetone was added to dissolve it completely. This was followed by addition of AEROPERL® 300 Pharma gradually, with rigorous mixing and stirring using magnetic stirrer for 30 minutes until uniform granules were formed. The system kept stable till excess of solvents got evaporate. Also ARTM+ AEROPERL® 300 Pharma SD were prepared using simple solvent evaporation method by dissolving drug into acetone completely with addition of AEROPERL® 300 Pharma slowly with stirring. The obtained solid dispersion granules were further studied for various analytical characterisation techniques.

Solubility Measurements

An excess quantity of ARTM was placed in 20 ml capacity test tubes containing 10 ml of different solutions (distilled water, 0.1 N HCl and phosphate buffer at pH 7.2) separately. The samples were sonicated for 20 min at room temperature and capped glass test tubes were shaken for 48 h at 37±0.1°C, speed 75 rpm using orbital shaking thermo stable incubator (Boekel Scientific, Germany). The solutions in the test tubes were vortexed and kept for centrifugation for 20 min at 10000 rpm. The supernatant solution was then filtered through a 0.45 µ millipore membrane filter and the amount of the drug dissolved was analyzed spectrophotometrically (UV-1601PC, Shimadzu, Japan) at 211 nm for ARTM after suitable dilution. All solubility measurements were performed in triplicate.

Saturation solubility study

To evaluate the solubility of ARTM in the presence and absence of AEROPERL® 300 Pharma or Lutrol F127 or Lutrol F68, saturation solubility measurements were conducted. An excess amount of plain ARTM and ARTM dispersions with AEROPERL® 300 Pharma, AEROPERL® 300 Pharma+ Lutrol F127, or AEROPERL® 300 Pharma+ Lutrol F68 in the ratios of 1:1, 1:2, and 1:3 were added to 20 ml of freshly prepared distilled water in clean test tubes and sealed in triplicate. Thereafter, the test tubes were shaken for 48 hrs at 37°C at a speed of 75 rpm on an orbital shaking thermo stable incubator (Boekel Scientific, Germany). Subsequently, the solutions were centrifuged at a speed of 10,000 rpm (Minispin, Eppendorf) for 10 minutes and the supernatant was filtered through a 0.45 µ millipore membrane filter. The filtered solutions were suitably diluted and analyzed for ARTM at 211 nm on a Jasco-V-530 UV spectrophotometer, using a validated UV spectrophotometric technique.

Phase solubility study

Phase solubility study was performed according to the method described by Higuchi and Connors[29]. An excess amount of ARTM was placed in 20 ml test tubes containing in 10 ml of

distilled water with different concentrations of AEROPERL® 300 Pharma separately. AEROPERL® 300 Pharma(1%, 2%, 3%, 4% and 5% w/v) for was used as hydrophilic polymer. In the formulation containing mixture of ARTM-AEROPERL® 300 Pharma-Lutrol F127 the equivalent % of Lutrol F127 (i.e. ratio of surfactant used in different SD formulations) was also added along with AEROPERL® 300 Pharma(1%, 2%, 3%, 4% and 5% w/v). In the formulation containing mixture of ARTM- AEROPERL® 300 Pharma-Lutrol F68 the equivalent % LutrolF68 (i.e. ratio of surfactant used in different SD formulations) was also added respectively along with AEROPERL® 300 Pharma(1%, 2%, 3%, 4% and 5% w/v).Test tubes were covered with cellophane membrane to avoid solution loss and then shaken (75 agitations/min) in orbital shaking incubator (Boekel Scientific, Germany) for 48 h at 37°C. The solutions in the test tubes were vortexed and kept for centrifugation for 20 min at 10000 rpm. 5 ml of supernatant was withdrawn and filtered through Whatman Filter Paper (Grade 1). The filtrates were analyzed using a UV–visible spectrophotometer at 211 nm after suitable dilution. All solubility measurements were performed in triplicate.

Assay of ARTM in Dispersion Granules

For the determination of ARTM content, dispersion granules or the crushed powder equivalent to 10 mg of ARTM, were weighed and extracted with 10 ml of methanol by vortex mixing for 5 min followed by centrifugation at10,000 rpm for 5 min on a Minispin Eppend of centrifuge. The supernatant was filtered through 0.45 µ Millipore membrane filter, and the filtered solutions were suitably diluted and analyzed for ARTM at 211 nm using a validated UV spectrophotometric method.

HPLC method development and validation

The assay of the SD was evaluated using high-performance liquid chromatography (HPLC) apparatus equipped with Binary HPLC pump, and 2998 Photodiode Array detector (Agilent Corporation, Milford, Massachusetts). A reverse-phase C18 column (150 × 4.6 mm; 5 µm particles) was used. The mobile phase was composed of water–acetonitrile (25:75, v/v)[30]. Samples equivalent to 20 mg of ARTM were dissolved in 5 mL of methanol and appropriately diluted and the drug content was determined by HPLC at $\lambda = 211$ nm. The method validated was found to be stable for acid, base, oxidation, reduction, heat degradation studies. Flow rate and injection volume was 1 mL/min and 20µ/l for. Inter- and intra-day coefficients of variation for ARTM were found to be ≤10%

Physical Characterization of Dispersion Granules

Differential Scanning Calorimetry (DSC)

Thermal characterization of ARTM and optimized dispersion granules was performed by Differential scanning calorimeter (DSC-PYRIS-1, Perkin Elmer, USA. Samples (4-8 mg) were sealed in aluminium pans for analysis. The DSC thermograms were recorded from 40°C to 120°C at a heating rate of 10°C/min. An empty pan was used as a reference. A nitrogen flow rate of 20 ml/min was used for each DSC run.

Powder X-Ray Diffraction (PXRD)

Powder X-ray diffraction patterns of ARTM and optimized dispersion granules were recorded to assess the solid state of ARTM, using a Phillips X-ray diffractometer with a copper target, voltage 40kV, current 20 mA, at a scanning speed of 20 per min.

Fourier Transform Infrared Spectroscopy (FTIR)

The KBr disks with ARTM and optimized dispersion granules were prepare dusing mechanically operated KBr Press Model HP-15. AJasco FTIR-5300 Fourier transform spectrophotometer was used to record IR spectra of the prepared discs, to confirm for any interaction of ARTM with excipients of dispersion granules.

Scanning Electron Microscopy (SEM)

The surface characteristics of samples were studied by scanning electron microscopy (SEM). Double sided carbon tape was affixed on aluminium stubs. The powder sample was sprinkled onto the tape. The aluminium stubs were coated with platinum plasma beam using JFC-1600 auto fine coater to make layer of 2 nm thickness above the sprinkled powder for 25 minutes. Then, these stubs were placed in the vacuum chamber of a scanning electron microscope. The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 Torr, acceleration voltage: 30.00 kV) XL 30. Model JEOL 5400 made in japan was used during analysis.

Dissolution Rate Studies

Dissolution rate studies were performed in triplicate for plain ARTM powder, three sets of nine formulations filled inside gelatine capsules, on a USP type-I dissolution tester (TDT-08L, Electrolab) in 1000 ml phosphate buffer of pH 7.2 with 1% sodium lauryl sulfate (SLS) at 37°C using the basket method at a rotation speed of 100 rpm for ARTM powder and dispersion granules. ARTM powder and samples of each formulation equivalent to 20 mg of ARTM were added to the dissolution medium. Aliquots (5 ml) were withdrawn and filtered at predetermined time intervals. The initial volume was maintained by adding 5 ml of fresh dissolution medium. The withdrawn samples were assayed for ARTM content after suitable dilutions at 211 nm using a validated UV spectrophotometric method.

Dissolution kinetic studies

Dissolution kinetic studies of prepared formulation were carried out using zero order, first order, Higuchi, Hixson Crowell and korsemeyer Pappas equation model. Regression coefficient factor (r^2) and other factors were calculated to understand the release kinetic behaviour of prepared SD formulations[31].

Flow Properties Measurement

Flow properties of the dispersion granules were determined by measuring the Carr's compressibility index (CI). Bulk density was calculated by measuring the volume of 5g of granules in a 50 ml measuring cylinder. The cylinder was tapped 100 times manually through a fixed height of 10 cm from the surface, till there was no further reduction in volume of the granules. Tapped density was calculated using the volume obtained after tapping. Carr's compressibility index values were determined. Optimized dispersion granules were also characterized for angle of repose; it was determined by allowing the dispersion granules to flow through a glass funnel of internal diameter 10 mm on the horizontal surface. The height (h) of the heap formed was measured, and the radius (r) of the cone base was also determined. The angle of repose (θ) was calculated.

Moisture uptake studies

A weighed amount of prepared SD about 100 mg were placed in crucibles at accelerated condition of temperature and humidity, 40 ±2 °C and 75 ± 5% RH respectively in environmental test chamber (Thermo lab, INDIA,). The changes in weight of samples were determined using Moisture balance MB 50C (CITIZEN, India)

RESULTS AND DISCUSSION

Statistical analysis

This proved the validity of model and equations as well, further ascertaining the effects of Lutrol F127, Lutrol F68 and AEROPERL® 300 Pharma on the dissolution and flow properties of dispersion granules. Three dimensional response surface plots and two dimensional contour plots were drawn from the data with Design Expert version 8.0.1.7 to estimate the effects of the independent variables on each response, as depicted in Figure (2-6).The circular shape of the contour plots indicates the nonlinear nature of the results.

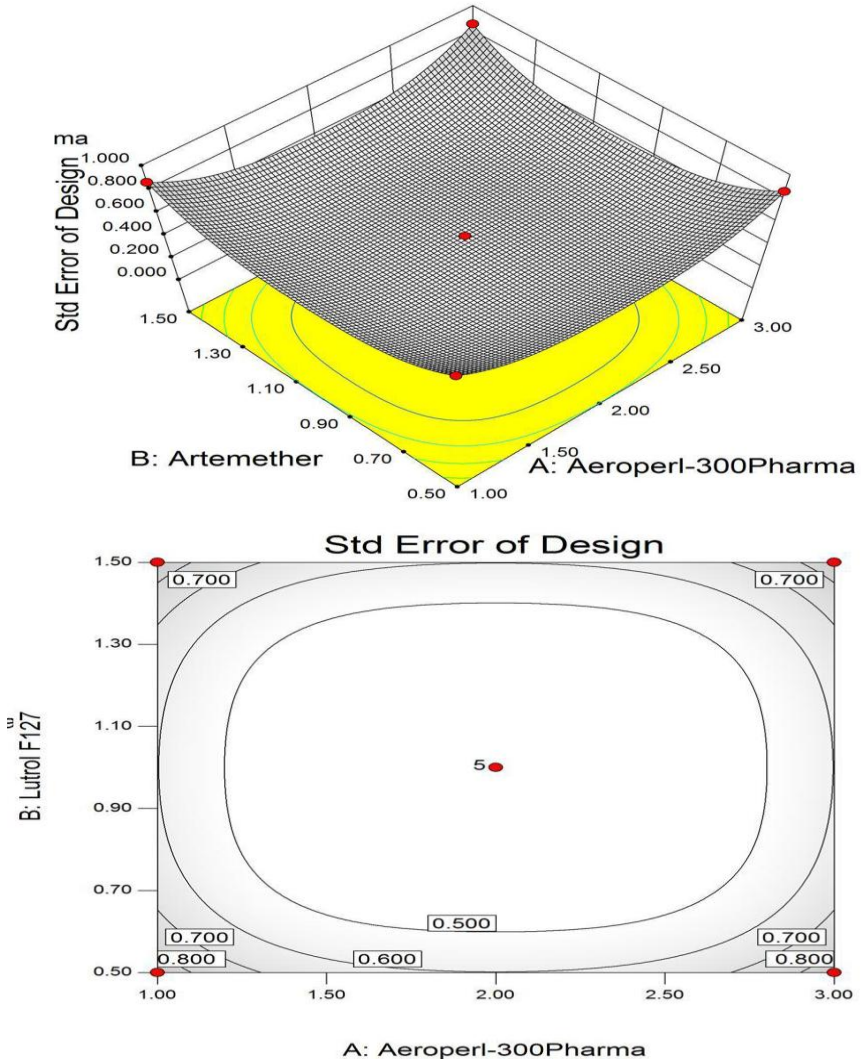
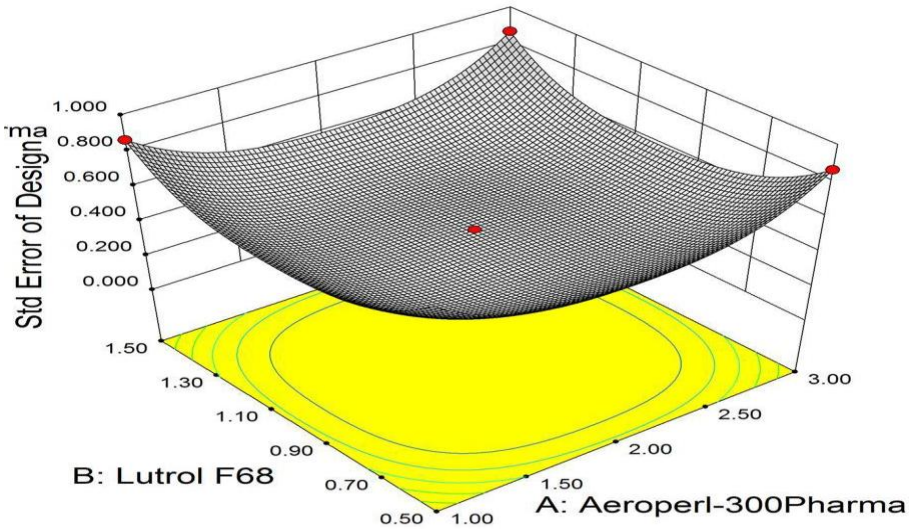


Figure (2-3) Surface and contour plots showing cumulative % release in first 60 min. of dispersion granules as a function of Lutrol F127 and AEROPERL® 300 Pharma



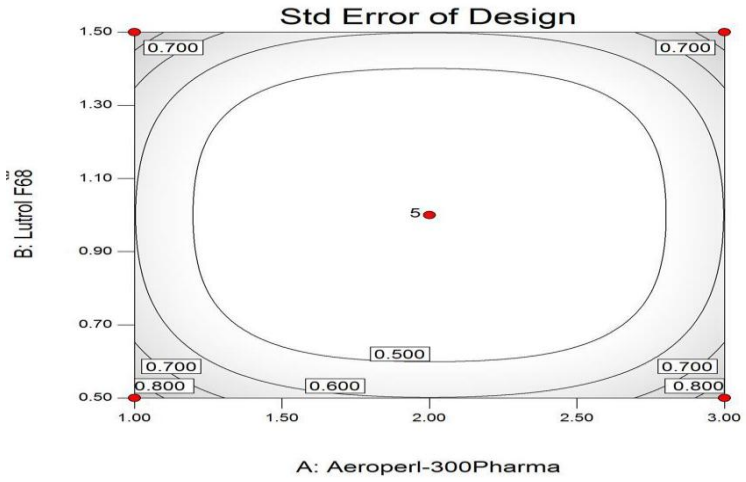


Figure (4-5) Surface and contour plots showing cumulative % release in first 60 min. of dispersion granules as a function of Lutrol F68 and AEROPERL® 300 Pharma.

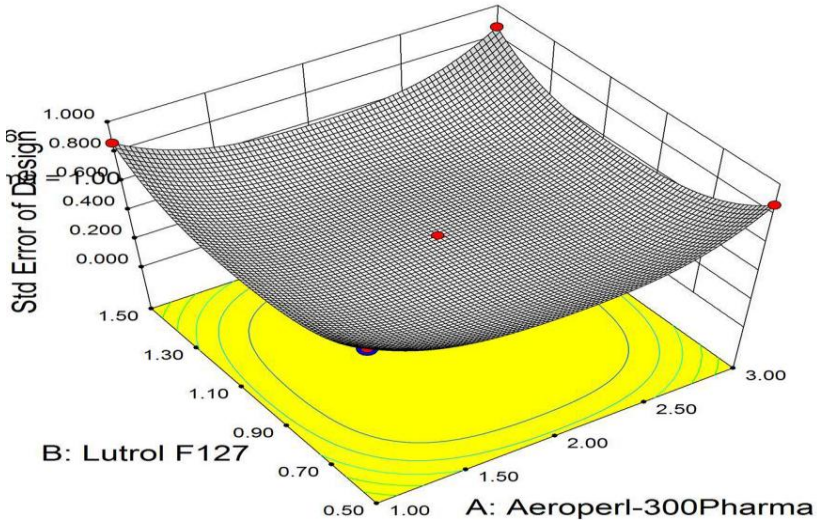


Figure 6 3D Surface plot showing the compressibility index of dispersion granules as a function of Lutrol F127 or Lutrol F68 and AEROPERL® 300 Pharma.

Solubility Measurements

The solubility of pure ARTM in distilled water was found to be 0.0183 µg/mL. A linear relationship with respect to increase in solubility of ARTM to increasing ratio ofAeroperl-pharma300 or Lutrol F127 or Lutrol F68 to drug was observed Figure7. This suggested the solubilising properties of Lutrol F127 or Lutrol F68 for ARTM. The 1:1, 1:2 and 1:3; drug: AEROPERL® Pharma 300 or (Lutrol F127+ AEROPERL®300 Pharma) or(Lutrol F68+ AEROPERL® Pharma 300) ratios enhanced the solubility of ARTM up to an extent of 0.12 mg/ml, 0.84mg/ml and0.75 mg/ml respectively. The increase in solubility in the presence of Lutrol F127 or Lutrol F68 could probably be explained by increased wettability of ARTM which could be because of a decrease in the interfacial tension between the drug and distilled water.

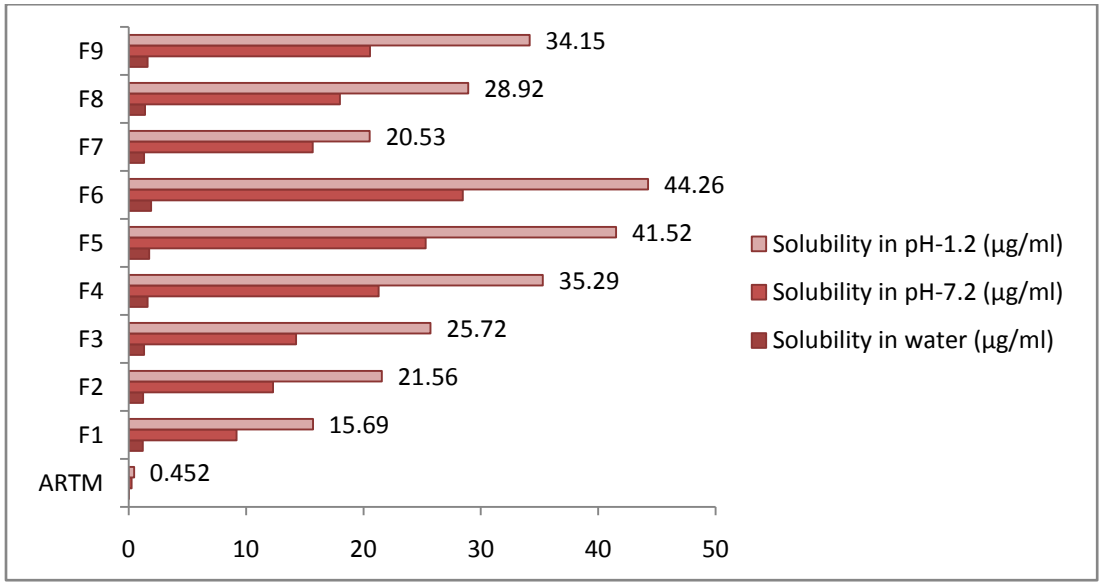


Figure 7 Solubility studies of prepared SD

Phase solubility study

The influence of AEROPERL® 300 Pharma, Lutrol F127 and Lutrol F68 on solubility of ARTM in distilled water at 37°C is presented in Figure2. The phase solubility diagram corresponds to ARTM type profiles. The enhancement in solubility might be due to the hydrophilic nature of surfactant and surface adsorption of drug on the surfactant Figure 8.

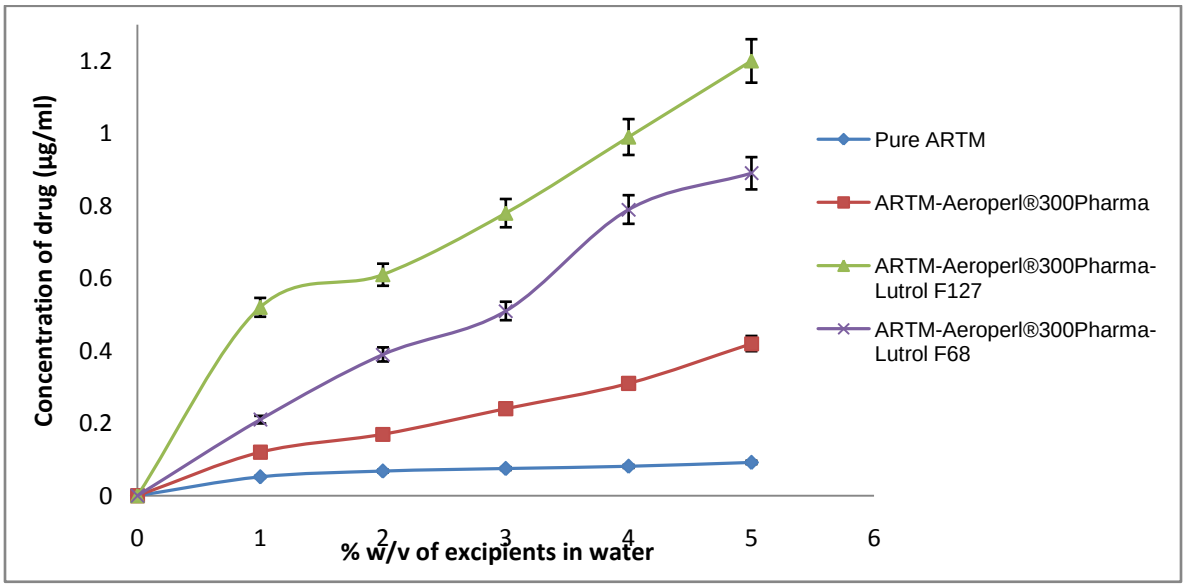


Figure 8 Phase solubility studies of prepared SD in water

HPLC Stability studies

The prepared SD kept for stability studies at 37°C at room temperature and 40°C/70 RH [relative humidity]. Samples were withdrawn at 3, 6 months and analyzed for drug content using validated HPLC method. Percentage drug content was in the range of 97.37 ± 0.81% to 99.15 ± 0.48% in

ARTM formulations. All determinations are mean ± SD [n = 3].HPLC chromatograph of pure ARTM shown in Figure 9.

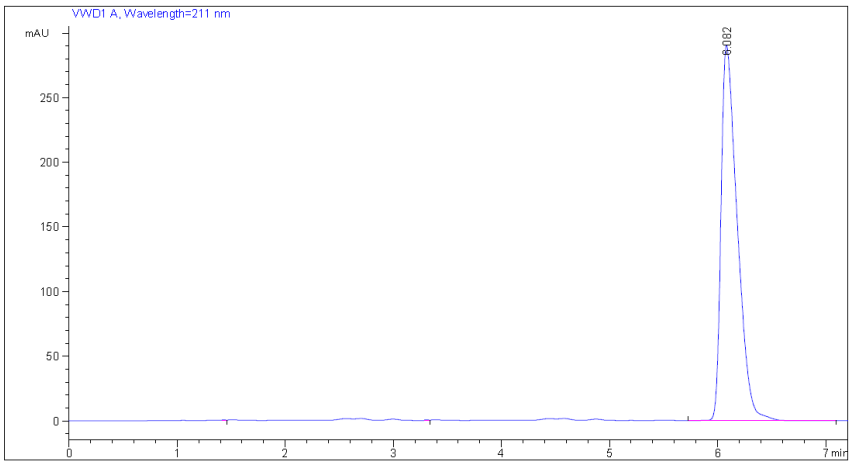


Figure 9 HPLC chromatogram of Pure ARTM

DSC studies

The DSC thermograms of pure ARTM and dispersion granules are represented in Figure 10. The DSC thermogram of ARTM showed a single endotherm at 90°C, which was ascribed to drug melting. The DSC thermogram of dispersion granules showed complete disappearance of ARTM endotherm which could be due to its amorphous nature contributed by Lutrol F127 or Lutrol F68 and AEROPERL® 300 Pharma or could be due to the dissolution of ARTM into the melt of Lutrol F grades. We could thus conclude that during scanning of temperature for the optimized dispersion granules; drug dissolves into the molten Lutrol F127 or Lutrol F68, starting from 51-60°C and is no more present in its undissolved form inside the system, when the melting temperature of ARTM is reached.

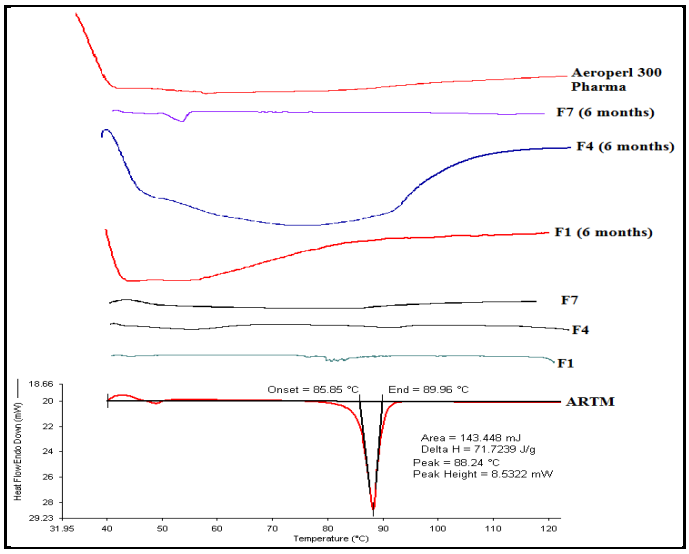


Figure 10 DSC of Prepared SD formulations

PXRD studies

PXRD pattern of ARTM indicate its crystalline nature and a 1:1 solid dispersion formulation indicate the retention of the amorphous form of ARTM in the matrix of Lutrol F127 or Lutrol F68**(**Figure 11).Furthermore the presence of AEROPERL® 300 Pharma could prevent the reversion of the amorphous drug to crystalline state on storage of the solid dispersion because of its amorphicity.

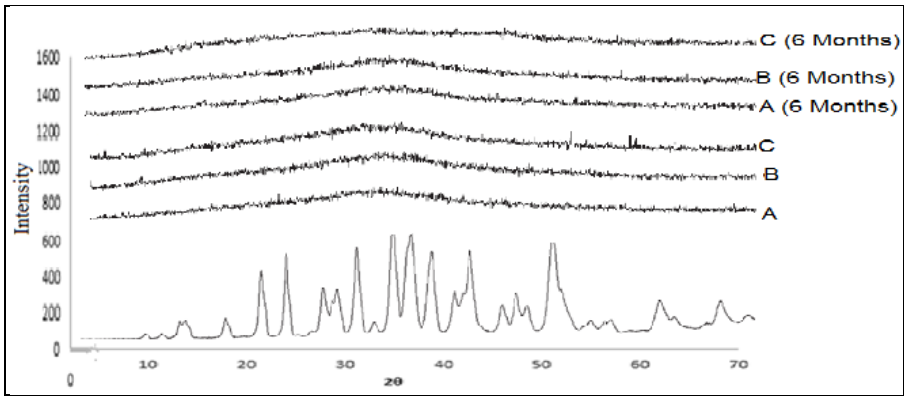


Figure 11PXRD of prepared SD formulations

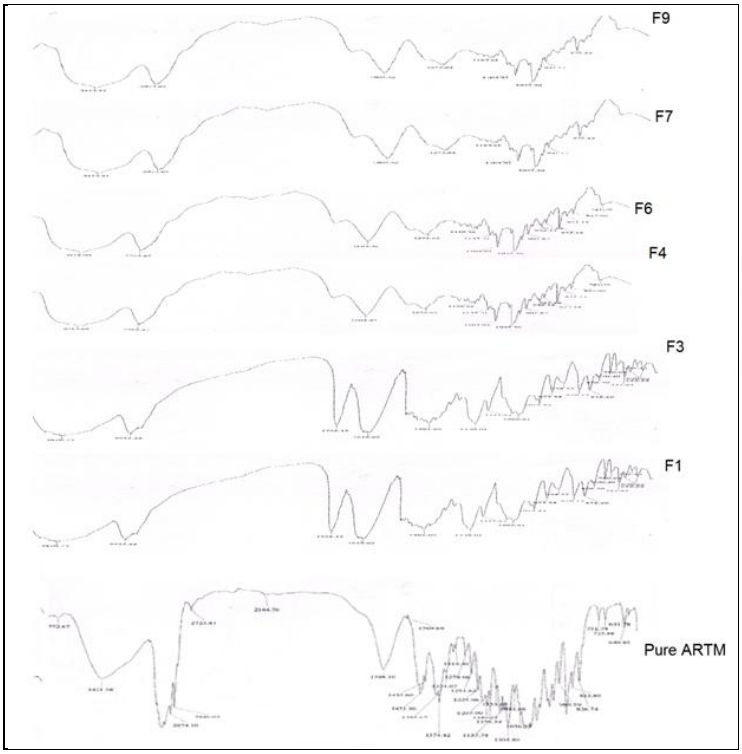


Figure 12IR of Prepared SD formulations

FTIR studies

Infrared spectra of ARTM as well as its ternary dispersion granules are presented in Figure 12. ARTM alone shows two carbonyl absorption bands at 1732 and 1602 cm^{-1}, assigned to the

carboxyl carbonyl and amide carbonyl stretching, respectively. These bands are of diagnostic value to elucidatedrug-excipient interactions. In the dispersion granules thecharacteristic carboxyl carbonyl band appeared unchanged,whereas the amide carbonyl stretching band was recorded at1649 cm^{-1}, a higher wave number than the drug alone. This behaviour could be attributed to some drug carrier interaction.The FT-IR spectra of dispersion granules showed almostall the bands of AEROPERL® 300 Pharma or Lutrol F127 or Lutrol F68, without affecting its peakposition and trends, which indicated the absence of well-defined interactions between ARTM and AEROPERL® 300 Pharma or Lutrol F127 or Lutrol F68 Figure12**.**AEROPERL® 300 Pharma (colloidal silicon dioxide) has silanolgroups on its surface, which make it a potential proton donor as well as an acceptor. The hydrogen bonding potential of silanols in the local environment on silica surfaces is well documented. Thus, hydrogen bonding between the drug under investigation (with proton accepting and/ or donating potential) and AEROPERL® 300 Pharma could be possible.

SEM analysis

SEM photographs exhibited a smooth and spherical shape of AEROPERL® 300 Pharma. Scanning electron microscope image of AEROPERL® 300 Pharma and optimized dispersion granules of ARTM. In case of dispersion granules the smooth surface of AEROPERL® 300 Pharma was transformed to a slightly rough due to the adsorption of the dispersion which contributed to a high dissolution rate because of enhanced effective surface area of ARTM. Moreover the adsorption of the melt on the adsorbent was uniform as almost all the smooth surfaces of the adsorbent particles Figure 13. The spherical shape of dispersion granules was confirmed by SEM which contributed to the good flow properties as very few sporadically formed particles were observed.

Dissolution studies

The dissolution rate and extent increased as compared to plain ARTM, with increase in the amount of AEROPERL® 300 Pharma or Lutrol F127 or Lutrol F68. Lutrol F127 or Lutrol F68 has an HLB value of 18-25 and is expected to solubilize the hydrophobic drug in the solid state. Similarly the dissolution of ARTM from dispersion granules prepared with various amounts of AEROPERL® 300 Pharma keeping the drug: Lutrol F127 or Lutrol F68 ratio constant at 3 levels, increased as compared to plain ARTM. This could be because of the increase in effective surface area over which the drug distribution increases accompanied by an enhancement in drug dissolution. Thus the observed dissolution rate enhancement could be attributed to the combined function of solid dispersion and surface adsorption which lead to enhanced wettability and an

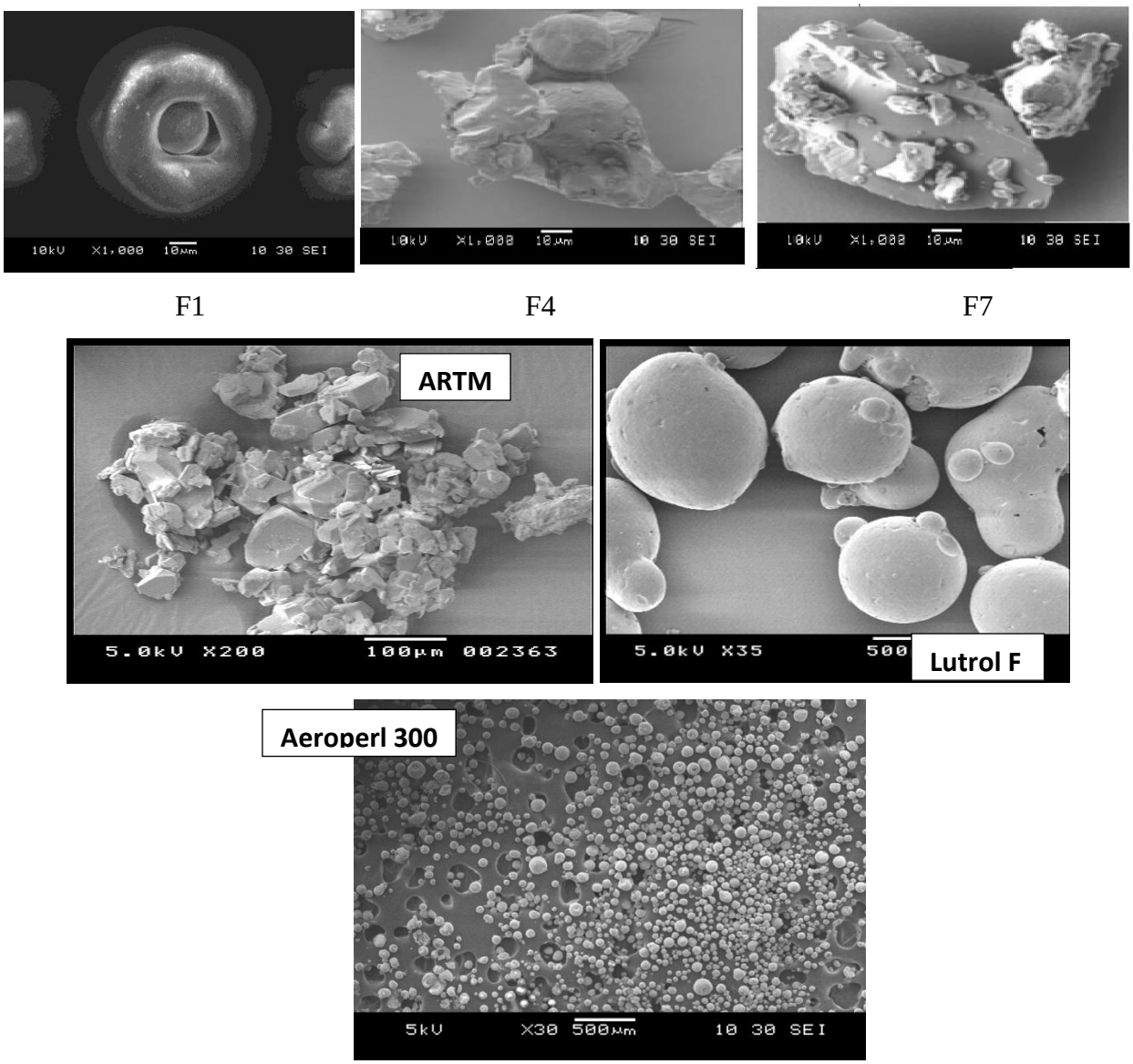


Figure 13 Scanning electron micrographs of prepared SD formulations

increased effective surface area of ARTM. However, the solid dispersion carrier seems more important for the initial enhancement of dissolution. The dissolution profiles of 3 sets of 9 formulations (n=9). Dissolution profiles of plain ARTM and optimized dispersion granules. Figures 14 show the dissolution profiles of various SD formulations and mixtures of ARTM with AEROPERL® 300 Pharma, AEROPERL® 300 Pharma -Lutrol F127 and AEROPERL® 300 Pharma -Lutrol F68 respectively. Because of the extreme low solubility of the drug, 1% (w/v) SLS was added to the dissolution medium. ARTM is a poorly soluble drug with a solubility of 0.0183 µg/mL in water. The saturation solubility of the ARTM was increased (be 0.12 µg/mL) by the addition of SLS to the dissolution medium. The dissolution of the SD formulation with AEROPERL® 300 Pharma (F1 = 42.5 %, F2 = 45.12 %, F3 = 51.29 % at the end of T60

minutes) was approximately 3.8, 4.1 and 5.2 fold higher than ARTM alone respectively. The dissolution of the SD formulation with AEROPERL® 300 Pharma-Lutrol F127 (F4 = 88.8 %, F5 = 90.17 %, F6 = 94.63 %, at the end of T60 minutes) and AEROPERL® 300 Pharma-Lutrol F68 (F7 = 75.47 %, F8 = 79.54 %, F9 = 80.63 %, at the end of T60 minutes)was approximately 8, 8.19, 8.60 and 6.86, 7.23, 7.33 fold higher than ARTM alone respectively. The increase in the dissolution rate in the case of the SD formulation is attributed to the amorphous state of the drug that offers a lower thermodynamic barrier to dissolution and the formation dispersion where the drug is molecularly dispersed inside the cavity of Aeroperl. The higher apparent solubility and increase in dissolution rate for amorphous materials is well known and has been extensively documented. The enhancement in solubility is the result of the disordered structure of the amorphous solid. Because of the short-range intermolecular interactions in an amorphous system, no lattice energy has to be overcome, whereas in the crystalline material, the lattice has to be disrupted for the material to dissolve.

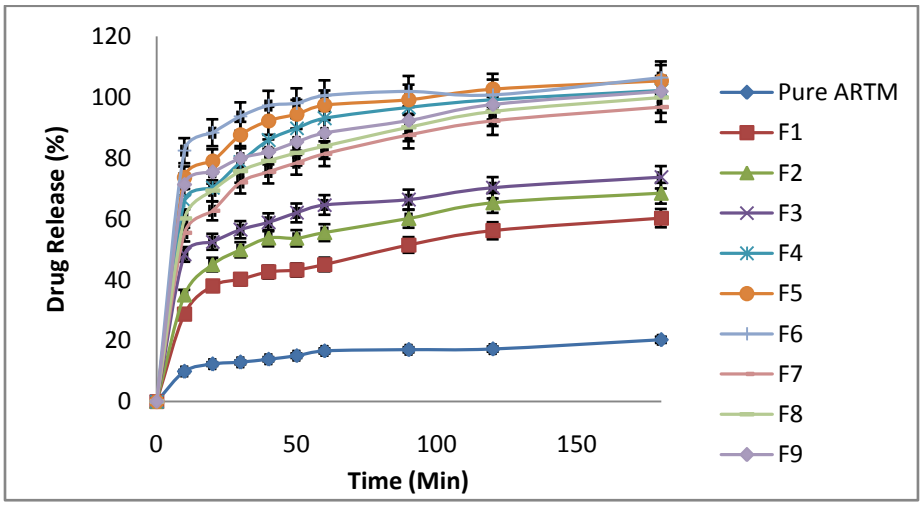


Figure 14 In vitro release of formulation batches from F1 to F9 at phosphate buffer pH7.2with1 % SLS[mean ± SD (n=3)]

Flow Properties Measurement

The calculated compressibility index of the optimized formulation was 11.69±0.18% to 18.08±0.12%, which falls in the range of excellent flow properties Table 2. This could be contributed by AEROPERL® 300 Pharma due to its good Flowability, high adsorbing capacity for the sticky Lutrol-ARTM melt, and uniform spherical shape. The angle of repose for these dispersion granules was found to be 14±1.6° to 18±1.6°. If the angle exceeds 50°, the material would not flow satisfactorily, whereas materials having values below 30° flow easily and well. The rougher and more irregular the surface of the particles, the higher is the angle of repose.

Table 2 Flow properties of prepared SD formulations

Formulation Codes	(Angle of repose θ)	Hausners ratio	Carr's Index
F1	14.87	0.45	11.69
F2	14.85	0.48	12.92
F3	15	0.47	13.83
F4	16.68	0.53	12.41
F5	16.32	0.52	13.87
F6	16.03	0.76	13.62
F7	17.33	0.84	16.07
F8	17.21	0.85	17.75
F9	16.06	0.83	18.08

Moisture uptake studies

Moisture uptake study is conducted to check hygroscopic nature of the prepared SD. No significant change in weight was observed after subjecting the sample to accelerated conditions of temperature and humidity. The accelerated stability studies showed that there was no considerable change in drug content during study duration. Drug content was found to be almost same as initial 99%.

Dissolution Kinetics

The dissolution kinetic studies were carried out and the best suited results obtained in the case of Higuchi equation model. The value of R^2 in Higuchi model is nearer to 1 and thus we conclude that dissolution followed Higuchi order kinetics **Table 3.**

Table 3 Dissolution kinetics of prepared SD formulations

Formulation Types	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Hixon–Crowell (r^2)	Krosmeyer–Peppas (r^2)
F1	0.7562	0.680	0.9958	0.4097	0.9357
F2	0.6755	0.731	0.9967	0.4427	0.9678
F3	0.5895	0.811	0.9979	0.4580	0.9376
F4	0.6425	0.905	0.9937	0.5759	0.9756
F5	0.6117	0.814	0.9954	0.6065	0.9670
F6	0.5721	0.847	0.9976	0.6441	0.9603
F7	0.6431	0.747	0.9920	0.5174	0.9646
F8	0.6487	0.729	0.9940	0.5269	0.9681
F9	0.6630	0.654	0.9982	0.5391	0.9639

CONCLUSION

A combination of solid dispersion and surface adsorption could be used effectively to enhance the dissolution of a poorly water-soluble drug, i.e. ARTM. The solid dispersion carrier, Lutrol F127 or Lutrol F68 played a significant role in the initial enhancement of drug dissolution. The surface adsorbent AEROPERL®300 Pharma imparted very good Flowability to dispersion

granules. The ternary dispersion granules could thus be easily encapsulated with high drug loading without any processing problems, which are usually associated with solid dispersions. It can be concluded that the applicability of Lutrol F surfactant in third-generation solid dispersions prepared by melt adsorption technology may be regarded as a good technique with which to accelerate the dissolution of poorly soluble drugs such as ARTM. Besides improving dissolution, surfactants can also enhance absorption, thereby increasing the bioavailibility of poorly soluble drugs.

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