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Comparison of Two Grafted Copolymers, Soluplus and Kollicoat IR, as Solid Dispersion Carriers of Arteether for Oral Delivery Prepared by Different Solvent-Based Methods

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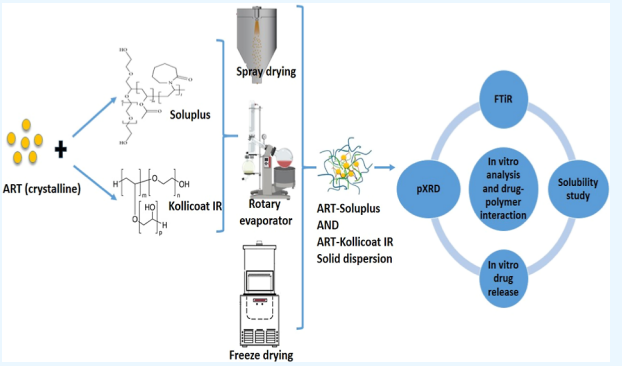
Cite This: https://doi.org/10.1021/acsomega.3c04110

ABSTRACT: Arteether (ART), an antimalarial drug, belongs to BCS class II and has very low oral bioavailability. Clinically, it is given as a solution in oil by the intramuscular route. Solid dispersion in Soluplus or Kollicoat IR, two commonly used grafted copolymers, may improve its in vitro dissolution and oral bioavailability. ART solid dispersion was prepared by three solvent-based methods: rotary evaporation (ethanol as solvent), spray drying (hydro-alcoholic solvent), and freeze-drying (aqueous solvent). ART-polymer miscibility increases with increasing polymeric concentrations up to 4% or 6%. Spray drying resulted in the highest increment of ART saturation solubility (476.01 ± 10.01 mg/L) than that of rotary evaporation (432.22 ± 15.76 mg/L) or freeze-drying (122.97 ± 2.94 mg/L) in the drug-Soluplus (1:1 w/w) ratio. Also, with Kollicoat IR-based solid dispersion, the same trend was observed. The drug-polymer ratio of 1:3 (w/w) showed a decrease in saturation solubility. Spray-dried products were better for flow properties (Carr index: 21.27 ± 0.98 for the 1:1 ratio of drug-Soluplus solid dispersion) than the other two methods. An enteric-coated capsule was prepared with an ART-Soluplus (1:1) ratio, selected based on the saturation solubility and downstream feasibility compared with those of Kollicoat IR. Eudragit L-100-coated enteric capsules containing 100 mg equivalent ART showed 88.88 ± 2.9% drug release in phosphate buffer pH 6.8 medium, which is significantly higher than that in raw drug (<10%) and a physical mixture of the exact composition of solid dispersion (44%). The study concluded that Soluplus possesses better properties as a solid dispersion carrier than those of Kollicoat IR. A stable, partially amorphous solid dispersion of ART was developed that can provide improved oral bioavailability.



1. INTRODUCTION

Malaria is the most prevalent parasitic disease and the foremost cause of morbidity and mortality worldwide. As per the World Malaria Report 2021, published by the World Health Organization (WHO), the cases of malaria globally in 2020 were estimated at 241 million, with an increase of 14 million from 2019.[1] In 2020, malaria was endemic in 85 countries, out of which, 29 countries accounted for malaria cases and deaths globally.[1] The most highly pathogenic of the four malarial parasites is *Plasmodium falciparum*, which infects humans. The most difficult-to-control malaria vector is *Anopheles gambiae*.[2]

Currently, the recommended therapy for uncomplicated malaria is based on an artemisinin-type compound, either monotherapy or combined with another drug.[3] Artemisinin, or qinghaosu, is a lactone sesquiterpene extracted from sweet wormwood or *Artemisia annua*. Active against all species of Plasmodium, artemisinin is a potent blood schizontocide of rapid action compared with other antimalarials.[4] The therapeutic value of artemisinins is desirable as the occurrence of multidrug-resistant strains is increasing. Several artemisinin derivatives have been developed for their clinical applications. The list includes dihydroartemisinin, artemether, artesunate, and arteether. These derivatives have significant activities against malaria parasites. More importantly, they are highly effective against chloroquine-resistant malarial parasites.[5] Arteether is an ethyl ether derivative of dihydroartemisinin, which was developed as a novel semisynthetic antimalarial drug in the late 1980s.[6] Arteether had a significant curative effect against the erythrocytic stage of chloroquine-resistant Pseudomonas falciparum and cerebral malaria. Arteether is reported to have higher antimalarial activity than that of other artemisinin derivatives such as artemether and artesunate.[7]

Received: June 10, 2023
Revised: November 12, 2023
Accepted: November 15, 2023

Arteether possesses very low solubility (approximately 17 μg/mL)[8] but high permeability, hence being classified under BCS class II. Due to very slow dissolution and gastric decomposition, arteether shows poor and irregular absorption when delivered by an oral route.[9] It is delivered only by an intramuscular route. The need for oral formulations is evident in improving patient compliance. Arteether was formulated as solid lipid nanoparticles (SLN)[5] and a self-emulsifying drug delivery system (SEDDS) for oral delivery.[2] Both approaches could enhance the oral bioavailability of arteether. However, they have their drawbacks, such as the complexity of the SLN formulation or the high surfactant content of SEDDS. Solid dispersion is another popular approach to enhancing the dissolution of the poorly water-soluble drug.[10,11] For BCS class II drugs with dissolution rate-dependent oral absorption, the solid dispersion approach can significantly improve their oral bioavailability.[12,13] There are more than 30 US FDA-approved drug products based on the solid dispersion approach, and the number is increasing yearly.[14] In amorphous solid dispersion (ASD), the active ingredient is dispersed in a substantially amorphous form within an excipient matrix. The amorphous state of the drug in ASDs is responsible for enhanced solubility and dissolution.[15] The role of the excipient matrix or carrier matrix, which is generally a hydrophilic polymer, is significant in ASD. The polymeric carrier plays multiple roles in an ASD formulation, such as preventing recrystallization during storage, increasing the wettability of the drug, and preventing drugs from precipitating in a supersaturated state.[14]

Several polymers are used as hydrophilic excipients or carriers in solid dispersion. The list includes synthetic or semisynthetic polymers, such as polyvinylpyrrolidone (PVP), poloxamer 188 or 407, hydroxypropyl methylcellulose (HPMC), and natural polymers such as different types of gums, chitosan, etc. Recently, vinylpyrrolidone-vinyl acetate copolymers (Kollidon)[16] and HPMCAS (HPMC acetyl succinate)[17] have become popular solid dispersion carriers. A binary mixture of polymers is often used, such as PVP K30-PEG 6000,[18] PVP K30-poloxamer,[19] etc.

Two graft copolymers found their application as solid dispersion carriers: one is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (brand name: Soluplus) and the other is poly(vinyl alcohol)-polyethylene glycol graft copolymer (brand name: Kollicoat IR). Soluplus, originally developed by BASF, Germany, is considered an excellent hydrophilic solubilizer.[20] Since the past few years, Soluplus has mainly been used to formulate solid dispersion with many BCS class II and class IV drugs such as felodipine,[21] famotidine,[22] efavirenz,[22] gliclazide,[11] etc. Kollicoat IR is also a BASF (Germany) product and is indicated as a multifunctional polymer with ideal instant-release coating properties that can also be applied for binding, drug layering, and pore-forming applications.[23] Although fewer than Soluplus, Kollicoat IR has been used with miconazole[24] and itraconazole[25] to formulate solid dispersion for better dissolution.

In this study, both Soluplus and Kollicoat IR have been used to develop an arteether solid dispersion formulation for oral delivery. Three different solvent evaporation methods are used: freeze-drying for the aqueous solvent, spray drying, and rotary vacuum evaporation for the organic solvent to prepare solid dispersions. Different polymers' and preparation techniques' effects are evaluated using an experimental design. The final selected formulation was loaded into an enteric-coated capsule. This study is the first report comparing two grafted copolymers as solid dispersion carriers with respect to different preparation methods.

2. RESULTS AND DISCUSSION

2.1. Drug-Polymer Miscibility. Arteether miscibility with Soluplus and Kollicoat IR was determined using the Gibbs free energy equation. Apparently, the result showed an increase in drug miscibility with an increase in the polymer concentration (Table 1). Soluplus has shown a linear increase in drug miscibility with an R^2 value of 0.947, whereas Kollicoat has not shown a proportionate increase. At 6% concentration, the miscibility of arteether was less than 4%. Between the two graft copolymers, Soluplus has resulted in significantly higher miscibility with arteether than that of Kollicoat IR at 1 and 2% concentrations. However, at 4% concentration, no statistically significant difference was observed (p-value: 0.653, analyzed by "student's t-test by ANOVA") between the two polymers.

Table 1. Miscibility between Arteether and Two Copolymers

	Kollicoat IR	Soluplus
concentration of polymer (%w/v)	ΔG (kJ/mol)	
1%	−11.33	−13.8
2%	−12.81	−13.9
4%	−14.76	−14.86
6%	−13.9	−15.07
intercept	1.18	2.46
slope	37.11	41.52
K_a	0.86	0.41

All the ΔG_t^0 values (kJ/mol) were negative, and the lowest values of −14.76 and −15.07 were obtained with 4% for Kollicoat IR and 6% for Soluplus, respectively. This result implied that the process could be more effective in higher polymeric concentrations. For drug-polymer miscibility, the total Gibbs free energy should be ideally less than zero or negative. Proper mixing induces disarrangement or disorders at the molecular level of two components. Thus, entropy is reduced, facilitating the mixing of two components.[26] The apparent stability constant K_a was higher in Soluplus than that in Kollicoat IR (Table 1). A higher K_a value indicates a more favorable interaction. A negative K_a value indicates an increase in solubility. In this case, positive K_a values signify the kinetic solubility of arteether in water in the presence of different polymers. Higher solubility is predicted from the amorphous state of a drug, which is indicated by K_a values. However, amorphous drugs may tend to recrystallize. Hence, K_a is known as the apparent stability constant.[27]

2.2. Methods of Preparation. Among the three techniques used in this study, spray drying should be the most appropriate due to its efficiency, scalability, less heat exposure of the drug, and acceptable final product characteristics. However, the percent yield in spray drying was relatively lower for small formulation batches. The yield of various spray-dried batches in this study was between 53.23 and 71.98%. In contrast, there was a higher percent yield (>94.23%) in freeze-dried batches. However, the dried products were too fluffy with a very low bulk density as we had not added any bulking agent. Rotary evaporation resulted in a 74.38−95.55% yield of the product. However, using an absolutely organic solvent as a vehicle could be a drawback of the system. Additionally, the

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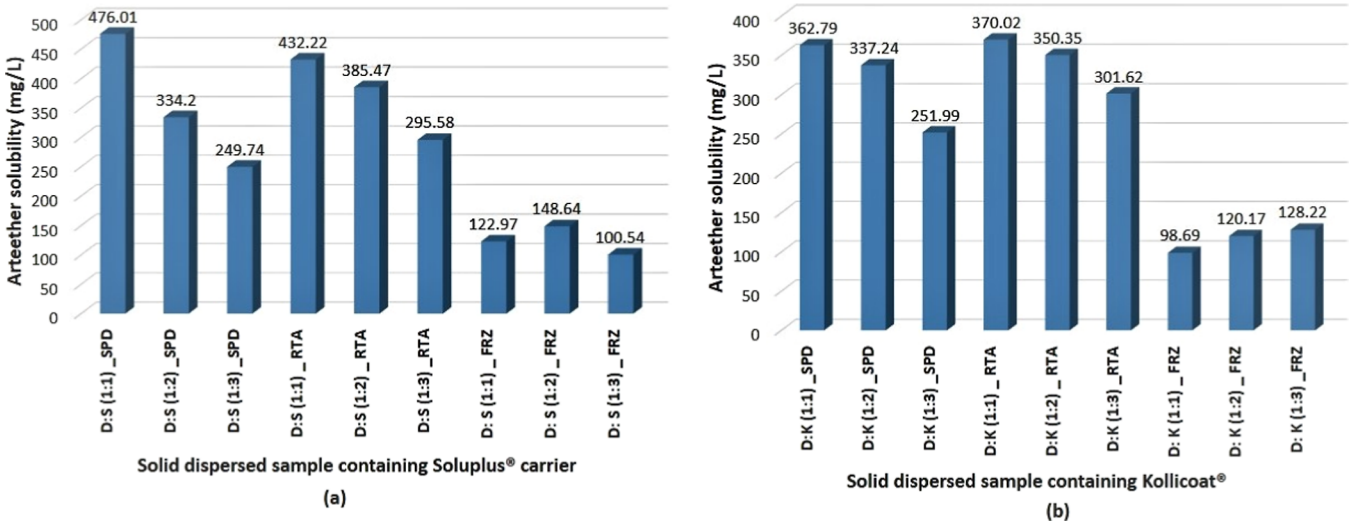

Figure 1. Arteether solubility in water from solid dispersions prepared by spray drying (SPD), freeze-drying (FRZ), and rotary evaporation (RTA): D/S-Drug/Soluplus and D/K-Drug/Kollicoat IR. The ratios given within parentheses indicate the drug-polymer ratio in grams: (a) solid dispersion with Soluplus and (b) solid dispersion with Kollicoat IR.

scalability of the rotary evaporation for preparing solid dispersions is questionable.

2.3. Saturation Solubility of Arteether—Soluplus and Arteether- Kollicoat IR Solid Dispersion and Drug Content Analysis. Arteether is poorly soluble in water. The reported aqueous solubility of the drug is 17 mg/L.[8] Arteether solubility was determined in our research to be 13.6 μg/mL. The aqueous solubility of arteether was significantly increased in the developed solid dispersion of both Soluplus and Kollicoat IR. Saturation solubility study results indicate a better solubility profile from the drug- Soluplus solid dispersion than that from the drug-Kollicoat dispersion. The results of the saturation solubility of arteether solid dispersion in Soluplus and Kollicoat IR are shown in Figure 1a,b, respectively.

The drug content in all solid dispersions was within a range of 92.13−97.27%. The lowest drug content was found in the rotary evaporated solid dispersion in both polymeric carriers. In rotary evaporation, the extraction of solid-dispersed powder from the round-bottom flask after drying resulted in product loss, which might cause low drug content. In spray drying, product losses also took place. The highest drug content (95.68%) from the spray-dried solid dispersion was obtained from arteether-Soluplus (1:1) and the lowest (93.08%) from arteether-Kollicoat IR (1:3). The freeze-dried solid dispersion displayed higher drug content with the highest value of 97.27% (arteether-Soluplus, 1:1) and the lowest of 94.27% (arteether-Kollicoat IR, 1:1). However, there was no significant difference in drug content among all batches of the formulation.

2.3.1. Comparison between Soluplus and Kollicoat for Solubility Enhancement. The arteether-Soluplus (1:1) solid dispersion resulted in statistically significant (p-value < 0.05) higher saturation solubility of the drug than that in the drug-Kollicoat solid dispersion prepared by all three different methods. For example, by spray drying, the drug Soluplus (1:1) showed 476.01 ± 10.01 mg/L arteether solubility compared to 362.79 ± 5.38 mg/L from the drug Kollicoat IR (1:1). The higher hydrophilicity of Soluplus could be one reason. However, in increased drug/polymer ratios, such as 1:2 or 1:3, there was no statistically significant difference (p-value > 0.05) in arteether solubility between Soluplus and Kollicoat IR solid dispersion carriers prepared by spray drying or rotary evaporation.

With the enhancement of the carrier ratio, from 1:2 to 1:3, in either Soluplus or Kollicoat IR, the drug solubility decreased from a 1:1 ratio. However, there was no significant difference (p value > 0.05) in drug solubility between the drug/polymer 1:2 and 1:3 ratios. At a higher arteether-carrier ratio than 1:1, Soluplus and Kollicoat IR might form a gel-like layer that inhibits the diffusion of aqueous medium or drugs through the carrier matrix.

2.3.2. Comparison between Different Methods of Solid Dispersion. Arteether solubility from solid dispersions prepared by different methods was compared, and a mixed observation was noted (Figure 1a,b). Spray-dried and rotary-evaporated solid dispersions resulted in statistically similar drug concentrations in the saturation solubility study. Both were higher than freeze-dried samples. Arteether/Soluplus (1:1) solid dispersions prepared by spray drying and rotary evaporation resulted in 476.01 ± 10.01 and 432.22 ± 15.76 mg/L, respectively. Both methods displayed statistically similar arteether solubility enhancement (p value > 0.05). Similarly, drug-Kollicoat IR (1:1) solid dispersions prepared by spray drying and rotary evaporation showed a similar arteether (p value > 0.05) solubility of 362.79 ± 5.38 and 370.02 ± 3.75 mg/L, respectively. A similar trend was observed in higher drug-polymer ratios. However, freeze-drying showed significantly low arteether solubility irrespective of either Soluplus or Kollicoat IR and regardless of the drug-polymer ratio. Statistical comparison of solubility data between freeze-drying and either spray drying or rotary evaporation showed significant differences (p value < 0.05). The reason is the use of organic solvents in spray drying and rotary evaporation but not in freeze-drying. In spray drying and rotary evaporation, an entire quantity of arteether was dissolved in the organic solvents before being subjected to mixing with polymer or polymeric solution, followed by evaporation. However, in freeze-drying, no organic solvent was used. Arteether was mixed by an overhead homogenizer in the aqueous polymeric solution, followed by prefreezing and drying. It is very likely that due to extreme hydrophobicity, arteether was precipitated

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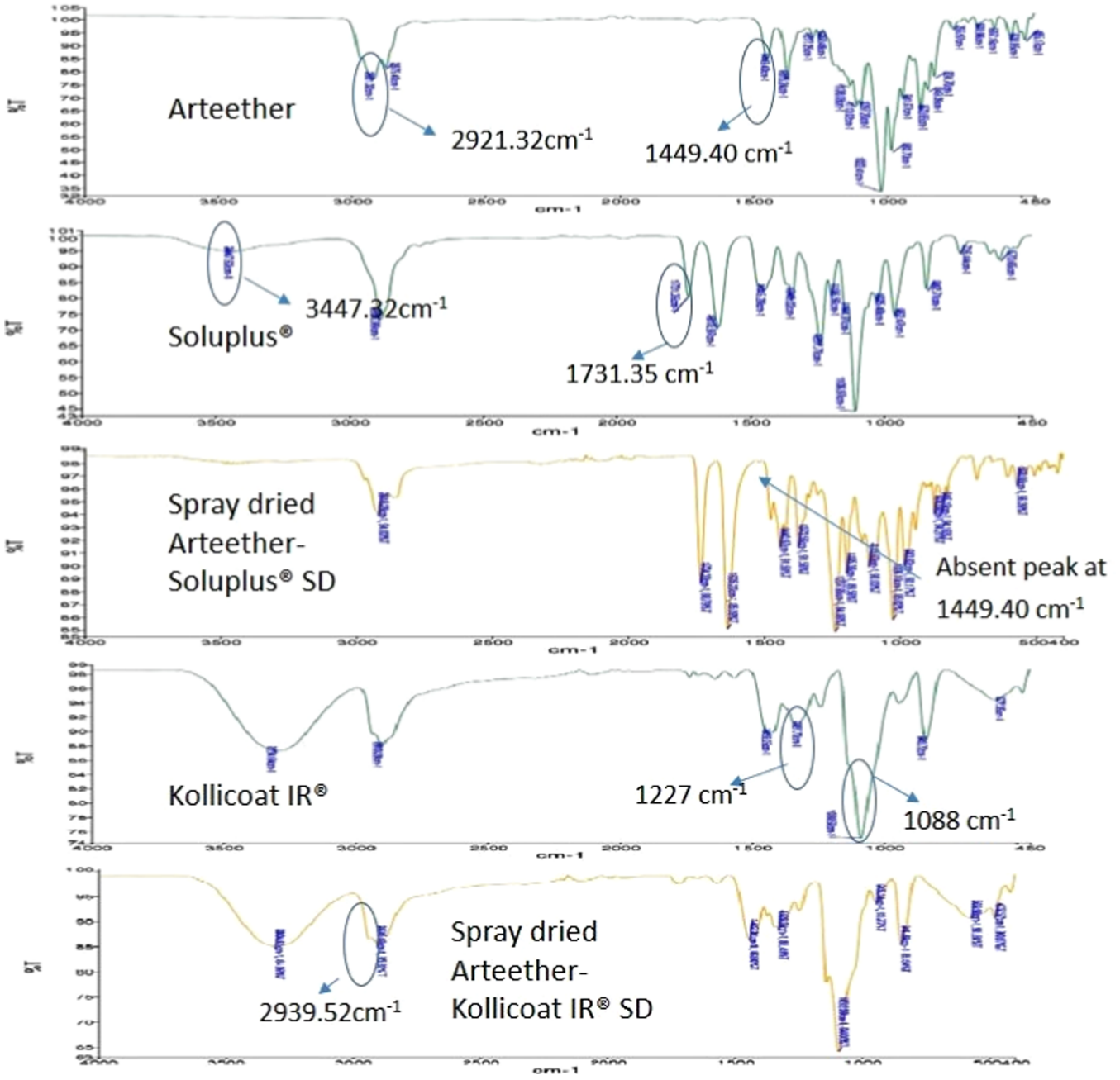

Figure 2. Infrared spectra of the pure drug, a physical mixture of drug/each individual polymer (1:1 w/w), and a solid dispersion of drug/polymer (1:1) prepared by spray drying.

out from the aqueous vehicle during prefreezing. That phenomenon could be responsible for the lesser conversion of crystalline arteether to amorphous, resulting in low solubility enhancement. Between spray drying and rotary evaporation, although both are solvent evaporation methods, the former uses fewer organic solvents than the latter. Also, spray drying is a scalable, industrially acceptable method compared to rotary evaporation for solid dispersion preparation. Hence, we have selected the spray drying method for our further development.

Comparison between different drug-polymer ratios showed that arteether-Soluplus or arteether-Kollicoat IR showed similar levels of solubility enhancement in 1:1 and 1:2 ratios. However, in the 1:3 drug-polymer ratio, arteether saturation solubility was found to be decreased in both Soluplus and Kollicoat IR. After a particular concentration, polymers can form self-micelles and a gel-like network that hinders drug solubility or dissolution. Based on the saturation solubility study, a spray-dried 1:1 drug-polymer (either Soluplus or Kollicoat IR) was selected for further evaluation.

2.4. Functional Group Interaction between Arteether and Polymers by FTIR. Infrared spectroscopic analysis evaluated the functional group interaction between arteether and individual polymers in the spray-dried solid dispersion. The derived spectra are presented in Figure 2. Arteether is characterized by the IR peaks at 2921.32 cm^{-1} (alkane C−H stretching), 1449.40 cm^{-1} (C−H bending), and 1022.4 cm^{-1} (C−O−C bending). The characteristic IR peaks of Soluplus were observed at 3447.62 and 1449.40 cm^{-1} for O−H stretching and aromatic C−H stretching and bending, respectively. Similar wavenumbers were reported by the

https://doi.org/10.1021/acsomega.3c04110
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previous researchers.[28] In the carbonyl region, pure Soluplus displayed two peaks for ester carbonyl (1731.35 cm^{-1}) and tertiary amide carbonyl (1632.59 cm^{-1}).[21] In the spray-dried arteether−Soluplus solid dispersion, the arteether peak at 1449.40 cm^{-1}, responsible for C−H bonding, was absent, and the other two characteristic peaks shifted slightly with lower intensities. Shifting or absence of a peak responsible for the functional group indicates the drug-polymer interaction. Soluplus has both proton-accepting (−OH) and proton-donating groups (ester carbonyl and amide). H bonding might have taken place between the drug and any of these two proton-donating groups. It is also possible that C−O of the benzopyran ring of arteether forms H bonds with the proton-accepting −OH group of Soluplus.[29] Hence, the −OH bond intensity in the solid dispersion decreased significantly. H bonding is a favorable phenomenon for a stable solid dispersion. It restricts the molecular mobility of the drug and prevents recrystallization during storage. Kollicoat IR is characterized by peaks at wavenumbers 1227 cm^{-1} (C−O−C stretching of the alkyl ether group), 1088 cm-1 (C−O stretching), and 3390 cm^{-1} (O−H stretching).[25] However, the O−H stretching peak is overlapped by a broad band at 3100−3400 cm^{-1} that occurred due to adsorbed moisture. Like Soluplus, Kollicoat IR also has proton-accepting groups susceptible to H bonding. The spray-dried drug-Kollicoat solid dispersion displayed all three characteristic peaks of arteether (2921.32, 1449.40, and 1022.4 cm^{-1}) but with little shift and altered intensity. There is a possibility of arteether−Kollicoat interaction or H bonding between susceptible groups, but due to high overlapping in the region of IR spectra, it could not be confirmed.

2.5. Thermal Analysis of the Spray-Dried Solid Dispersion. Thermal analysis of spray-dried arteether, either Soluplus or Kollicoat IR (1:1), solid dispersion was done by the differential scanning calorimetry (DSC) technique. Derived thermograms are shown in Figure 3. Arteether showed a sharp endothermic melting peak at 71.20 °C in the thermogram, indicating its crystalline nature with a normalized enthalpy of 52.75 J/g (Figure 3). Apart from extreme lipophilicity, such a crystalline nature is a reason for water insolubility and poor dissolution. Soluplus, being an amorphous polymer, does not have a sharp melting endotherm but a reported glass transition at around 70 °C.[30] In this study, Soluplus showed a broad endothermic band around 80−100 °C responsible for eliminating adsorbed moisture. Kollicoat IR, due to polyethylene glycol and poly(vinyl alcohol) grafting, is semicrystalline in nature.[31] In this research, Kollicoat IR has also shown a broad band within 60−110 °C, possibly due to the liberation of adsorbed moisture. In the physical mixture thermogram, the arteether melting endotherm was slightly broadened but with a melting peak at around 73 °C, indicating the presence of arteether in the crystalline state in the mixture. Arteether−Kollicoat IR physical mixture displayed no distinct drug peak in the thermogram. However, a broad endothermic band within a range of 60−100 °C was observed, similar to the pure Kollicoat IR peak. It can be assumed that the arteether melting peak was overlapped by the broad endothermic band of Kollicoat IR.

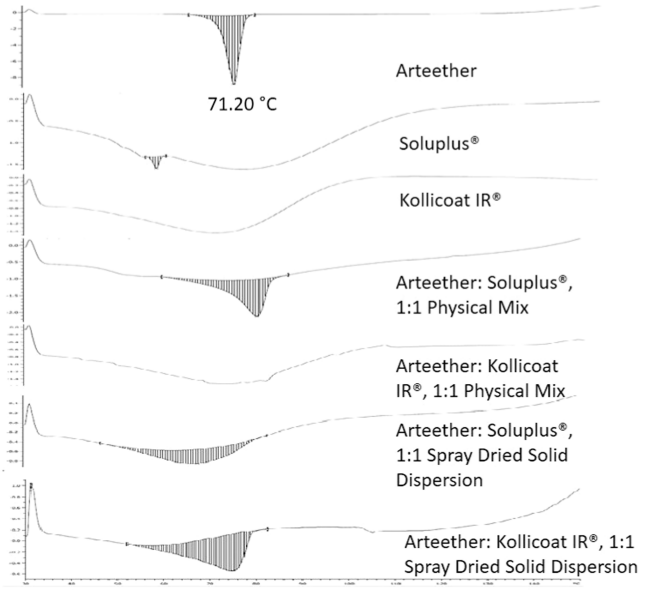

Figure 3. Thermogram of the pure drug, a physical mixture of drug/each individual polymer (1:1 w/w), and a solid dispersion of drug/polymer (1:1) prepared by spray drying.

In the thermogram of the solid dispersed 1:1 arteether−Soluplus spray-dried formulation, no sharp crystalline drug peak was visible, indicating the conversion of the crystalline drug to an amorphous form. Solid dispersed arteether in Kollicoat IR displayed a broad peak that was distinct from the physical mixture. It could be assumed that the presence of crystalline arteether displayed a broad peak. It may happen when a solid dispersion does not become fully amorphous. However, the conversion of the crystalline drug to the amorphous form in the Kollicoat IR-containing solid dispersion could not be confirmed from DSC analysis.

2.6. Selection of the Most Suitable Composition. Solubility enhancement of arteether was one of the main targets of this study. Based on the physical properties and solubility data, a spray-dried formulation of the drug/polymer (1:1 w/w) ratio was selected. Although the saturation solubility of arteether from the drug/Soluplus (1:1 w/w) solid dispersion was higher than the ratio of the drug-Kollicoat IR solid dispersion, flow property and compressibility study by determining the Carr index and Hausner ratio was carried out. The objective was to identify the most suitable formulation among the Soluplus and Kollicoat IR carriers. The Carr index and Hausner ratio values of Soluplus carrier-based solid dispersions were 21.27 ± 0.98 and 1.17 ± 0.02, respectively. The Kollicoat IR-based solid dispersion showed a Carr index and Hausner ratio of 29.81 ± 1.22 and 1.37 ± 0.03, respectively. These values showed that Soluplus resulted in better flow property and compressibility, which would be helpful in the downstream processing of the solid dispersion. Hence, spray-dried solid dispersion of arteether-Soluplus (1:1 w/w) was selected as the most suitable formulation for further evaluation.

2.7. Crystallinity Study by Powdered X-ray Diffraction. Powdered X-ray diffraction (PXRD) study provides sound evidence of the crystallinity of the drug present in a formulation mixture. The spray-dried arteether−Soluplus 1:1 w/w solid dispersion was subjected to crystallinity analysis. In the diffractogram of arteether (Figure 4), high-intensity peaks are observed at 10.33 and 18.81° 2θ angle with intensities of 15,357 and 13,382 cps, respectively. Sharp peaks of the drug confirm the crystalline nature, as analyzed by the DSC study. In the physical mixture of the drug and Soluplus, similar peaks

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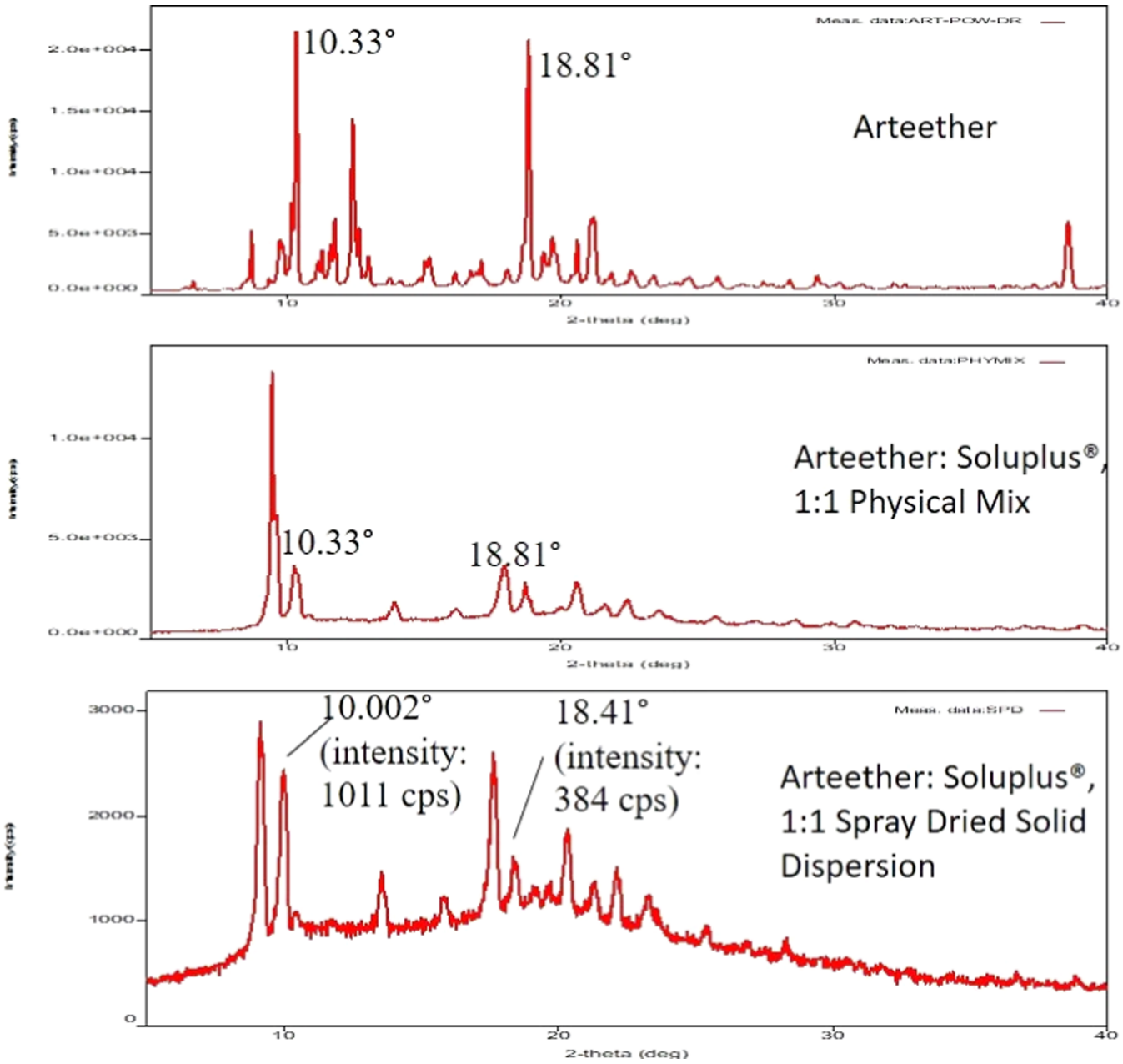

Figure 4. Powdered X-ray diffractogram of arteether, a physical mixture of arteether/Soluplus (1:1 w/w), and the arteether/Soluplus (1:1 w/w) solid dispersion prepared by spray drying.

are observed with reduced intensity and some broadening due to the presence of Soluplus in the mixture. In solid dispersion, characteristic arteether peaks are either absent or present with significantly low intensity compared to that of the pure drug or its physical mixture. Reduction in peak intensities indicates loss of crystallinity.[12] When a drug is dissolved in a solvent in the presence of a polymeric matrix, followed by solvent evaporation, it becomes dispersed in the polymeric matrix in either an amorphous or molecular dispersion form. Then the drug crystals do not remain in the matrix in their free form. Hence, sharp peaks due to the diffraction of X-rays by sharp angles are not observed.

2.8. Coating and Physicochemical Evaluation of the Final Dosage Form (Capsule). As the drug is susceptible to degradation in gastric pH, coated capsules loaded with solid-dispersed arteether in a Soluplus (1:1 w/w) carrier were prepared. Eudragit L100, a commonly used methacrylate polymer-coated capsule, showed no disintegration in an acidic medium (0.1 N HCl, pH 1.2) within 1.2 h. However, all capsules disintegrated in phosphate buffer pH 6.8 within 9.43−10.22 min. Hence, Eudragit L100 was selected for small intestine-targeted release. The target fill weight of the formulation in each capsule was 200 mg, equivalent to 100 mg of arteether. After filling, the weight variation of coated capsules was within the ±10% range of the mean weight. The assay of the capsules was found to be 96.23 ± 2.59%.

2.9. In Vitro Dissolution of Arteether Solid Dispersion-Loaded Capsules. An in vitro dissolution study was conducted to evaluate the cumulative percent drug release in the basic medium (phosphate buffer, pH 6.8) from arteether solid dispersion-loaded capsules. As shown in Figure 5, the arteether raw drug showed very poor dissolution in 2 h.

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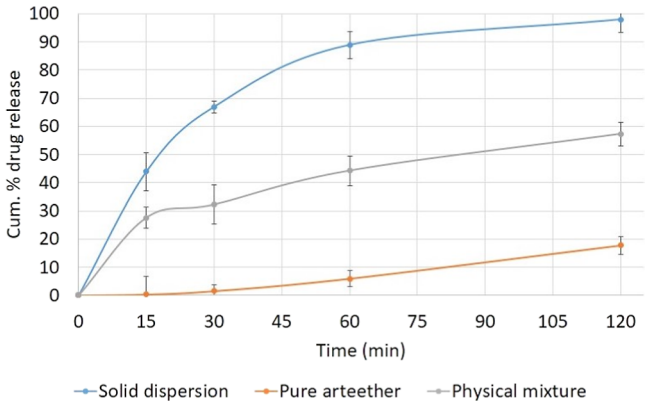

Figure 5. In vitro drug release (Cum. % release) of arteether, a physical mixture of arteether/Soluplus (1:1 w/w), and an arteether/Soluplus (1:1 w/w) solid dispersion prepared by spray drying in phosphate buffer pH 6.8.

Extreme lipophilicity hinders the dissolution of the drug. In a physical mixture, at 1 h, 44.23% drug release was observed. Soluplus, being a hydrophilic polymer, can influence the wettability of a drug and increase its dissolution to a certain extent. Other researchers report similar phenomena with Soluplus. The presence of Soluplus in the physical mixture showed a steady release of simvastatin of almost 90%, which was significantly higher than that of the bulk drug (41%).[32] In solid dispersion, arteether showed cumulative percent drug releases of 88.88 ± 2.9 and 97.93 ± 3.13% in 1 and 2 h, significantly higher than those of the raw drug and physical mixture. There are multiple reasons for such phenomena. I) The presence of a hydrophilic solubilizer improves the wettability and decreases the water repulsion of the lipophilic drug. II) The conversion of the crystalline drug to an amorphous nature increases the drug's solubility and dissolution. The energy of solubilization required in an amorphous system remains much lower than that in crystalline systems. The higher internal energy of amorphous drug molecules and increased molecular mobility favor faster and complete dissolution. III) The micellar solubilization property of Soluplus may also help in better dissolution. Arteether is a BCS class II drug with high intestinal permeability. Hence, it can be hypothesized that improved dissolution can provide better absorption after oral delivery.

Other dissolution parameters, such as DE_{30}% (dissolution efficiency at 30 min), DE_{120}% (dissolution efficiency at 120 min), and MDT (mean dissolution time), are presented in Table 2. The results showed a significant improvement in the dissolution parameters in solid dispersion. DE_{30}% of the solid dispersion displayed 57 times and 1.75 times more improvement than pure arteether and physical mixture. The arteether solid dispersion showed 9.73 and 1.89 times higher DE_{120}% than pure arteether and physical mixture, respectively. The MDT of the solid dispersion was 0.45 h, which is lower than that of the pure drug (1.2 h) and the physical mixture (0.58 h). It indicates lower retention of the drug and higher dissolution in the solid dispersion than those of the other two samples. In vitro dissolution results indicated that the arteether solid dispersion could generate a significantly better dissolution profile than that of the pure drug or its physical mixture.

Table 2. DE % and MDT of the Solid Dispersion, Pure Arteether, and Physical Mixture[a]

sample	DE_{30}%	DE_{120}%	MDT (hour)
SD	38.36	66.12	0.45
pure arteether	0.67	6.79	1.2
PM	21.82	35.03	0.58

[a]DE_{30}% (dissolution efficiency at 30 min), DE_{120}% (dissolution efficiency at 120 min), and MDT (mean dissolution time); SD: arteether solid dispersion; PM: physical mixture.

2.10. Stability Study. A short-term stability study was carried out under ambient and accelerated conditions. The in vitro dissolution study showed 92.33 ± 1.90 and 91.89 ± 2.3% drug releases from the arteether solid dispersion-loaded capsules kept in ambient and accelerated conditions, respectively, after 1 month. A significant challenge of solid dispersion formulation is the recrystallization of amorphous drugs.[33] Polymeric carriers such as Soluplus can prevent recrystallization by inhibiting the molecular mobility of the drug. If recrystallization happens, then the improvement of drug dissolution would be compromised. The short-term stability study in this research showed no statistically significant change (similarity factor, f_2 value > 85%) in drug dissolution while stored in different conditions. However, a full-scale stability study in appropriate conditions per the ICH guidelines must be carried out.

3. CONCLUSIONS

A comparative evaluation of the feasibility of preparing an arteether solid dispersion in two grafted copolymers was done. Soluplus and Kollicoat IR, both hydrophilic polymers, can improve drug solubility. Among the different solvent-based methods, such as spray drying, rotary evaporation, and freeze-drying, spray drying showed the highest solubility improvement in the 1:1 drug-carrier ratio. Among Soluplus and Kollicoat IR, Soluplus offers the highest solubility of arteether in a solid dispersion. A partially amorphous solid dispersion was formulated that can be converted to capsules for oral consumption. 100 mg of arteether/capsule can be used as a solid dispersion with more than 85% drug release in the small intestinal medium. As the drug shows dissolution-dependent absorption, improved dissolution could offer better oral absorption. At present, arteether is available as a solution in oil for intramuscular delivery. The development of oral delivery can increase patient compliance. The reported study provides in vitro evidence of improved arteether biopharmaceutical attributes (solubility) by solid dispersion in the Soluplus carrier.

4. MATERIALS AND METHODS

Themis Medicare, India, generously donated arteether (white wax-like consistency). Soluplus and Kollicoat IR samples were received as gift samples from BASF, Germany. Evonik, India, generously provided Eudragit L100, used as an enteric coating polymer. The rest of the reagents and chemicals used in the study were of analytical grade.

4.1. Miscibility Evaluation. Drug-polymer miscibility is an essential parameter of a monophasic solid dispersion. It was evaluated by the shake-flask method described by earlier researchers.[10] In separate glass vials, different concentrations (1, 2, 4, and 6% w/v in water) of each of the polymers, Soluplus and Kollicoat IR, were taken. An excess amount of ether was added to each. The vials were shaken by an orbital

https://doi.org/10.1021/acsomega.3c04110
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shaker for 24 h at 100 rpm, 37 ± 2 °C temperature. Aliquots were withdrawn, centrifuged at 8000 rpm, and filtered through 0.45 μ nylon syringe filters. The filtrates were processed by a predeveloped acid degradation method for arteether.[34] As arteether has very low sensitivity in UV wavelengths, the samples were converted to degradation products that can be quantitated by UV spectroscopy. The method was checked for linearity, specificity, accuracy, and precision. In short, the arteether sample was degraded by strong (5 M) hydrochloric acid in a water bath at 50 °C for 30 min. The product was quantitated at 254 nm by UV spectroscopy.

Following the analysis of the miscibility samples, the data were fit into the Gibbs equation to calculate the free energy transfer (ΔG_t^0) of arteether from pure water to the aqueous polymeric solution as follows[12]

$$(\Delta G_t^0 = -2.303RT \log(S_0/S_S)) \quad (1)$$

where R, T, and S_o/S_s are universal gas constants, the temperature in Kelvin, and the ratio of the molar solubility of the drug in aqueous polymeric solution to that of pure water without polymer, respectively. The apparent stability constant (K_a) was also determined using the following equation

$$k_a = \frac{\text{slope}}{\text{intercept}(1 - \text{slope})} \quad (2)$$

where the slope and intercept were derived from the plot of the mean drug concentration in polymeric solution (mg/mL) versus the respective polymer concentration (% w/v).

4.2. Experimental Design for Preparing Solid Dispersions. A 3^2 (three levels, two factors) factorial design was used for studying the effect of Soluplus and Kollicoat IR on arteether solubility in a solid dispersion. The design resulted in 9 formulations for each polymer. The composition of all experimental runs is presented in Table 3. The amount of either Soluplus or Kollcoat IR was used in three different ratios with respect to 1 g of arteether. Three solvent evaporation methods, such as spray drying, freeze-drying, and rotary evaporation, were used to prepare solid dispersions. With each polymer, 9 experimental batches were prepared.

Table 3. Composition of 18 Experimental Batches with Different Polymers and Prepared by Different Methods

batch code	arteether (gm)	Soluplus (gm)	Kollicoat IR (gm)	preparation method
F1	1	1		spray drying
F2	1	2		freeze-drying
F3	1	3		rotary evaporation
F4	1	1		rotary evaporation
F5	1	2		spray drying
F6	1	3		freeze-drying
F7	1	1		freeze-drying
F8	1	2		rotary evaporation
F9	1	3		spray drying
F10	1		1	spray drying
F11	1		2	freeze-drying
F12	1		3	rotary evaporation
F13	1		1	rotary evaporation
F14	1		2	spray drying
F15	1		3	freeze-drying
F16	1		1	freeze-drying
F17	1		2	rotary evaporation
F18	1		3	spray drying

4.3. Preparation of Experimental Solid Dispersion Batches. The experimental batches were prepared by one of the three methods as described below.

4.3.1. Spray Drying. The required quantity of polymer, either Soluplus or Kollicoat IR, was dissolved in water, and arteether was dissolved in the minimum possible quantity of methanol. Both solutions were mixed under stirring and dried in a lab-scale spray dryer using the following parameters: suspension feed flow rate 1 mL/min, air inlet temperature 130 °C, air outlet temperature 75 °C, and aspirator speed 55.

4.3.2. Freeze-Drying. This technique was nonaqueous and solvent-free. The required quantity of polymer, either Soluplus or Kollicoat IR, was dissolved in water. Arteether was added to the polymeric solution and stirred by an overhead stirrer for 1 h at 1000 rpm to make a uniform dispersion. The samples were prefrozen at −50 °C, followed by drying at −20 to 25 °C with a ramp of 1 °C/min. The total time of drying was 15 h at 0.08 mbar vacuum. Then, the obtained product was passed through sieve no. 40 and stored under a desiccator for further analysis.

4.3.3. Rotary Evaporation. The required quantity of drug and either Soluplus or Kollicoat IR were dissolved in the minimum possible quantity of absolute ethanol. An overhead stirrer stirred the solution at 1000 rpm for 10 min. The solvent was then evaporated by a rotary evaporator at 60 °C under vacuum. The dried sample was kept at room temperature for 12 h for further removal of residual solvents. The dried sample was sieved through sieve no. 40 and stored under a desiccator for further analysis.

4.4. Characterization of Experimental Batches. All of the experimental batches have been characterized by several in vitro evaluation studies.

4.4.1. Functional Group Study. The functional groups' interaction between arteether and two graft copolymers used in the study was evaluated by infrared spectroscopy (IR) using the attenuated total reflectance (ATR) technique (PerkinElmer, Spectrum 3). 2−3 mg of each of the samples (arteether, Soluplus, Kollicoat IR, a physical mixture of arteether-individual polymer in a 1:1 ratio, and developed solid dispersions) was placed on the diamond crystal of the ATR instrument and scanning was done in the IR wavenumbers (450−4000 cm^{-1}) range. Derived spectra were analyzed visually for functional group interaction.

4.4.2. Thermal Analysis. DSC was performed to determine the thermal properties of the developed formulations. 2−3 mg of the sample was weighed accurately and transferred to an aluminum crucible. The crucible was thermally treated in DSC equipment (Mettler TA 4000) by heating at a scanning rate of 10 °C per min from 30 to 150 °C. Derived thermograms were analyzed visually to identify the change in the physical state or any interaction.

4.4.3. Saturation Solubility Study. The saturation solubility of arteether in solid dispersions was determined using an orbital shaker. In glass vials, an excess amount of the sample was taken, and 5 mL of distilled water was added. The vials were kept in an orbital shaker for 24 h at 100 rpm rotation and 37 °C temperature. Aliquots were taken, filtered through 0.45 μ syringe filters, and analyzed for drug content by UV spectroscopy after acid degradation, as stated in Section 4.1.

https://doi.org/10.1021/acsomega.3c04110
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4.4.4. Drug Content Analysis. The drug content in different solid dispersions was determined by extracting arteether using ethanol. 10 mg equivalent to arteether was taken from each solid dispersion and added to 10 mL of ethanol with continuous stirring for 1 h. Aliquots were taken, centrifuged, and filtered. The supernatant was analyzed for drug content using the UV spectroscopy method described in Section 4.1.

4.5. Selection of Final Formulation. The final formulation was selected based on two criteria: the highest solubility and the advantages of the processing technique.

4.6. Crystallinity Analysis by X-ray Diffraction (XRD) of the Selected Composition. The final formulation was analyzed by powder XRD for crystallinity analysis. A PXRD instrument (Rigaku Ultima-IV, Japan) was used to scan the samples from 0 to 70° at 5°/min speed using Cu−K radiation at 40 kV voltage and 30 mA current to record diffraction angles (2θ) and intensity (counts). Derived diffractograms were analyzed and compared visually.

4.7. Preparation of the Final Dosage Form (Capsule). The final dosage form of the most suitable arteether solid dispersion was a capsule.

4.7.1. Density and Flow Property Analysis of Capsulating Mixture and Filling into Shells. Bulk density, tapped density, and angle of repose of the final arteether solid dispersion were determined using compendia techniques.[35] Standard equations described in earlier literature or monographs were followed[36] to calculate the Carr's index and angle of repose. The formulations were then categorized based on their flow property and compressibility.

The solid dispersion formulation was filled into a hard gelatin capsule size "00" using a manual capsule filling equipment. The target weight fill of each capsule was equivalent to 65 mg of arteether.

4.7.2. Coating of Capsules. Arteether is susceptible to gastric degradation. Hence, an enteric coating was necessary. Solid dispersed arteether capsules were coated by a lab-scale pan coater using Eudragit L100 as the pH-sensitive coating polymer. The composition of the coating solution was Eudragit L 100:5%, titanium dioxide:2.8%, diethyl pthalate:2.2%, acetone:30%, and isopropyl alcohol:60%. A 3% weight gain after coating was targeted.

4.7.3. Physicochemical Evaluation of Capsules. Coated capsules were evaluated by standard in vitro physicochemical parameters, such as capsule thickness-diameter, weight variation, and disintegration time. Standard methods described in previous articles and pharmacopoeia were followed for those characterizations. For the assay, 20 capsules were taken, and their contents were emptied, followed by mixing in a glass pestle by a mortar. The required amount of sample was taken and dissolved in 50 mL of methanol by continuous stirring by a magnetic stirrer to get a theoretical concentration of 50 μg/mL. Aliquots were taken, filtered through a 0.45 μ syringe filter, and analyzed by a predeveloped high-performance liquid chromatography (HPLC) method. The HPLC system consisted of an Agilent LC pump (LC-20AD) equipped with a UV−vis detector (SPD-M20A). The output signal was monitored and processed using Lab Solution Software (Version 6.83). Chromatographic separation was achieved on a 5 mm Agilent C18 Kromasil column (4.6 mm × 250 mm) in isocratic mode. Other chromatographic parameters were as follows: mobile phase: water/acetonitrile (30:70 v/v), flow rate: 1.5 mL/min, sample injection volume: 10 μL, and wavelength of detection: 216 nm.

4.7.4. In Vitro Dissolution of Capsules. In vitro dissolution of the capsules was performed in a USP Type I (basket) dissolution apparatus in phosphate-buffered medium (pH 6.8). The dissolution method parameters were 100 rpm speed of the basket rotation, 900 mL of media volume, 37 ± 2 °C temperature, 15, 30, 60, and 120 min sampling points, and 5 mL of aliquots taken at each point. The fresh dissolution medium was replaced in the dissolution basket immediately after each sampling to maintain the sink condition. The samples were analyzed by the HPLC method described in Section 4.7.3. The selected batch of solid dispersion-filled capsules containing 100 mg equivalent to arteether was analyzed for in vitro dissolution and compared with raw arteether (100 mg)-loaded capsules. The cumulative percent drug release concerning time was plotted from the quantitated data. The dissolution efficiency at 30 and 120 min (DE_{30}% and DE_{120}%) and MDT were calculated using eqs 3 and 4, respectively.[37] The derived values were compared between the solid dispersion, pure arteether, and physical mixture.

$$DE = \frac{\int_0^t y \, dt}{y_{100} \times t} \times 100 \tag{3}$$

$$MDT = \frac{\sum_{j=1}^{n} t_j^* \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \tag{4}$$

where y = area under the dissolution curve from time 0 to "t", y_{100} is 100% drug release at time t. j is the sample number, n is the number of samplings, t^* is the midpoint time of two sampling intervals between t_j and t_{j-1}, and ΔMj is the additional amount of drug dissolved between t_j and t_{j-1}.

4.8. Stability Study. A short-term (1 month) stability study was conducted in accelerated (40 °C/75% RH) and ambient conditions. At 0 and 1 month time points, the capsule dissolution and drug release were measured. The similarity factor (f_2) was calculated between the dissolution profiles of '0' month and '3' month data points using eq 5.[37] Two profiles are considered similar if f_2 becomes >50 and close to 100.

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n}(R_j - T_j)^2\right]^{-0.5} \times 100\right\} \tag{5}$$

where n is the sampling number and R and T are the percent dissolved of the reference and test products at each time point j, respectively.

4.9. Statistical Analysis. All of the studies were conducted in triplicate, and the results are expressed as mean ± standard deviation. Comparison between each data set was done using Student's t-test. p-values < 0.05 were considered significant in data analysis.

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https://doi.org/10.1021/acsomega.3c04110
ACS Omega XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank SVKM's NMIMS for providing the experimental facility for this study. The authors also wish to acknowledge Gitam School of Pharmacy, Gitam University, Hyderabad, for helping with the completion of this manuscript.

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