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Solid Dispersions of Artemisinin in Polyvinyl Pyrrolidone and Polyethylene Glycol

Stała dyspersja artemizyniny w poliwinylopirolidonie i glikolu polietylenowym

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Abstract

Background. Artemisinin (ARMN), a sesquiterpene lactone with an endoperoxide bridge (C-O-O-C), is an active anti-malarial moiety for drug-resistant malaria, which is spreading by 15% per annum in Pakistan. A few pharmacokinetic studies have indicated that ARMN is incompletely absorbed after oral intake due to poor dissolution characteristics in the intestinal fluids.
Objectives. To prepare ARMN formulations by physical mixing, solid dispersion and lyophilized dispersion techniques, using polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) in various proportions, to improve the pharmaceutical properties of the drug and to characterize the formulations' physicochemical properties.
Material and Methods. Solid dispersions of ARMN in mixtures of biopolymers – i.e., PVP and PEG – were prepared by three different methods and their pharmaceutical properties were evaluated. Different molecular weights of PVP (K30 and K25) and PEG (PEG6000 and PEG4000) were used in different drug-to-carrier ratios (1 : 9, 2 : 8, 3 : 7, 5 : 5 and 6 : 4). X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) were used to evaluate drug/carrier interactions in the solid state. The dissolution rate and equilibrium solubility were compared with corresponding physical mixtures.
Results. Based on the XRD results, pure artemisinin showed a completely crystalline structure. Solid dispersions of ARMN showed more amorphous structures than physical mixtures. Improvement in the drug dissolution rate was observed for solid dispersion formulations compared to physical mixtures. The dissolution rate and equilibrium solubility were enhanced as the polymer content increased. The lyophilized solid dispersions showed the highest dissolution as compared to all the other formulations. The order of decrease in dissolution rate was LYO > SD > > PM > Pure ARMN. This may be due to the nature and extent of the physical interaction between the drug and the carrier. This work indicates that the rate of artemisinin dissolution can be increased substantially by formulating it as a solid dispersion in PVP K30 using the lyophilization method. The addition of superdisintegrants such as PEG to the solid dispersions played an important role in the enhancement of the dissolution rate and thus in the preparation of fast-dissolving ARMN tablets **(Adv Clin Exp Med 2010, 19, 6, 745–754)**.

Key words: solid dispersion, artemisinin, PVP, PEG.

Streszczenie

Wprowadzenie. Artemizynina (ARMN), lakton seskwiterpenowy z mostkiem endonadtlenkowym (C-O-O-C) jest aktywną grupą funkcyjną przeciw lekoopornej malarii, która rozprzestrzenia się w Pakistanie o 15% rocznie. Niektóre badania farmakokinetyczne wykazały, że ARMN po podaniu doustnym nie jest w pełni wchłaniana z powodu słabej rozpuszczalności w płynach jelitowych.
Cel pracy. Przygotowanie preparatu ARMN za pomocą mieszania fizycznego, stałej dyspersji i technik liofilizowanej dyspersji, z użyciem poliwinylopirolidonu (PVP) i glikolu polietylenowego (PEG) w różnych proporcjach. Poprawa właściwości farmaceutycznych leku i scharakteryzowanie właściwości fizykochemicznych preparatu.
Materiał i metody. Stałą dyspersję ARMN w mieszaninach biopolimerów, tj. PVP i PEG, przygotowano 3 różnymi metodami i oceniono ich właściwości farmaceutyczne. Użyto różnych mas cząsteczkowych PVP (K30 i K25) i PEG (PEG6000 i PEG4000) w różnych stosunkach lek–nośnik (1 : 9, 2 : 8, 3 : 7, 5 : 5 i 6 : 4). Za pomocą dyfrakcji rentgenowskiej (XRD) i spektroskopii fourierowskiej (FTIR) oceniono interakcje lek–nośnik w stanie stałym. Porównano szybkość rozpuszczania i równowagę rozpuszczalności z odpowiadającymi im mieszaninami fizycznym.

Wyniki. Na podstawie badań XRD stwierdzono, że czysta artemizynina miała strukturę całkowicie krystaliczną. Stałe dyspersje ARMN wykazały bardziej amorficzne struktury niż mieszaniny fizyczne. Poprawę szybkości rozpuszczania leku zaobserwowano w przypadku preparatów stałej dyspersji w porównaniu z mieszaninami fizycznymi. Szybkość rozpuszczania i równowaga rozpuszczalności były lepsze w miarę wzrastania zawartości polimeru. Liofilizowane stałe dyspersje rozpuszczały się najlepiej w porównaniu z innymi preparatami.
Wnioski. Tempo rozpuszczania w porządku malejącym to LYO > SD > PM > czysta ARMN. Tak może być ze względu na charakter i zakres fizycznych interakcji między lekiem a nośnikiem. Praca ta wskazuje, że szybkość rozpuszczania artemizyniny można zwiększyć, łącząc ją jako stałą dyspersję w PVP K30 metodą liofilizacji. Dodanie znakomitych dezintegratorów, takich jak PEG, do stałych dyspersji odegrało ważną rolę w poprawie szybkości rozpuszczania, a tym samym w przygotowaniu szybko rozpuszczającej się tabletki ARMN **(Adv Clin Exp Med 2010, 19, 6, 745–754)**.

Słowa kluczowe: artemizynina, stała dyspersja, poliwinylopirolidon, glikol polietylenowy.

Malaria is vector-borne and is one of the major killer diseases in the world, causing an estimated one to two million deaths annually [1]. Recently it has been observed that malarial cases occur throughout the year in the Sindh Province [2, 3]. The clinical symptoms of malaria are varied and non-specific, but commonly include fever, fatigue, malaise, headache, myalgia and sweating. Anemia is a common complication due to hemolysis; and in falciparum malaria, serious complications such as acute renal failure, pulmonary odema and cerebral dysfunction can occur [4]. Antimalerial drugs are commonly administered orally; however, these agents may be given parenterally for a quick therapeutic effect, followed by oral treatment [5].

Antimalarial drugs can be categorized according to the stage of the parasitic life cycle they impact. Blood schizonticidal agents like artemesinins arederived from Qinghaosu, obtained from *Artemisia annua* (also called sweet wormwood), used to treat acute malarial attack [5]. Various semi-synthetic drugs such as artemether, artesunate and arteether have been chemically derived from artemisinin. These drugs have been converted to oral, rectal and parenteral formulations [6]. Artemisinin is lipophilic in nature, thus can only be given orally [7]. However, the solubility of lipophilic drugs can be improved by preparing solid dispersions [8]. Solid dispersion involves the fine or molecular dispersion of lipophilic drugs in hydrophilic carrier substances, which results in the enhanced solubility of the drugs due to solubilization, particle size reduction or conversion into amorphous nature [8, 9]. Lyophilization is also used for enhancing drug solubility by molecular dispersion. It involves dissolving the drug with the carrier in a co-solvent, followed by their freezing and sublimation [10].

The current study was conducted to prepare artemisinin formulations as physical mixtures, solid dispersions and lyophilized dispersions, to improve the pharmaceutical properties of the drug.

Material and Methods

Material and Apparatus

Artemisinin was purchased from Alchem, India; polyvinylpyrrolidone (PVP)-K25 and K30 and polyethylene glycol (PEG)-4000 and 6000 were obtained from Fluka Chemicals Limited (USA). Methanol, acetone, potassium bromide and silica gel were procured from Merck (Germany). Other chemicals used were starch (Rafhan, Pakistan), lactose (DMV international, Netherlands), primogel (Yung-Zip Chemicals, Taiwan) and magnesium stearate (Royal Tiger Products, Taiwan).

The apparatus used included a lyophilizer and Rotavapor (Buchi, Japan), a pump (Vacuum brand, Germany), a tablet hardness machine (Curio, Pakistan), an oven (Ney, Germany), a water deionizer (Waterman, Pakistan) and a single punch compression machine (Curio, Pakistan).

Methods

Artemisinin and PVP K30, artemisinin and PVP K30 and K25, artemisinin and PVP K30 and PEG4000 and artemisinin and PVP K30 and PEG6000 were weighed in the ratios 1 : 9, 2 : 8, 3 : 7, 5 : 5 and 6 : 4, and were formulated by the following methods:

1. The Physical Mixture Method.
2. The Solid Dispersion Method.
3. The Lyophilization Method.

The Physical Mixture Method

A glass mortar and pestle was cleaned and dried thoroughly. Precisely weighed quantities of the drug and polymers were mixed in the ratios noted (1 : 9, 2 : 8, 3 : 7, 5 : 5 and 6 : 4), using the mortar and pestle for 5 to 7 minutes until a homogenous mixture was obtained. Then each mixture was passed through a sieve (80 μm diameter),

transferred to well dried bottles and stored at 25°C in a desiccator.

The Solid Dispersion Method

Precisely weighed amounts of the drug and polymers were transferred to 500 ml round flasks in the given ratios (1 : 9, 2 : 8, 3 : 7, 5 : 5 and 6 : 4), to which 100 ml of methanol was added. The flasks were fixed on the flask shaker (Yellow Line OS10 Basic) and shaken at 150 rpm for 24 hours at room temperature. Then the flasks were attached to the rotary evaporator to evaporate the methanol (approximately 75 ml). These mixtures were then transferred to petri dishes and placed in desiccators containing silica gel for drying. Once the drying was complete, the mixtures were gently ground, passed through a sieve (80 μm diameter), transferred to well dried bottles and stored at 25°C in desiccators.

The Lyophilization Method

The procedure is the same as described for the solid dispersion method up to the attachment to the rotary evaporator for complete evaporation of the methanol. At that point 100 ml of distilled water was added, the preparations were shaken well and placed in an electronic deep freezer at –60°C. Freeze drying was performed with the help of a lyophilizer. When these mixtures were completely dried, they were ground gently and passed through a sieve (80 μm diameter). These mixtures were then transferred to well dried bottles and kept at 25°C in a desiccator.

Tablet Preparation by Wet Granulation

Artemisinin tablets were prepared by the granulation method, by homogenous mixing of 200 g of starch and lactose along with the active ingredient. A slurry was prepared by mixing 50 g of starch in 100 ml of deionized water. Deionized water (150 ml) was boiled in a stainless steel container and added to the aforementioned mixture. The burner flame was reduced and the paste was gently stirred for 3 to 5 minutes. The prepared paste was added to the mixed powder of starch and lactose. Mixing was carried out for 20 to 30 minutes. The prepared grains were passed through a sieve (mesh size 8) and dried in a hot air drier for 35 minutes. The half dried granules were passed through a sieve (mesh size 20) and then dried for 15 minutes at 70°C. When the moisture content of the granules was less than 1%, they were preserved in a polythene bag. The different granule preparations were mixed thoroughly with 5% of primogel as a disintegrant, magnesium stearate as a lubricant and 120 mg artemisinin to get homogenous mixtures, which were compressed into tablets by a single punch machine in a controlled humidity area (relative humidity less than 40%). The different tablet formulations were labeled properly and stored in sealed bottles.

Dissolution Studies

Drug release was measured using a dissolution paddle apparatus (Galvano Scientific, Pakistan). The dissolution medium (500 ml) consisted of water (90% v/v), ethanol (10% v/v, to increase drug solubility maintaining sink conditions during dissolution) and sodium lauryl sulphate (0.1% w/v) and was stirred at 50 rpm and 37°C. For every dissolution experiment, an amount of formulation equivalent to 120 mg of artemisinin was used. At predetermined time intervals, 5 ml samples were taken after filtration through cellulose acetate filter (Sartorius AG, Goettingen, Germany) with 0.45 μm pore size, and were replaced with the same volume of fresh medium. The alkali reactions of filtered dissolution samples were tested and analyzed spectrophotometrically at 290 nm [11, 12].

FTIR Analysis

Fourier transform infrared spectroscopy (FTIR) of all formulations was conducted by the KBr method [13] with 0.5–1% of sample in 200 mg KBr discs, using a FTIR spectrophotometer (Shimadzu, Japan). The scanning range was 450–4000 cm^{-1}.

X-Ray Diffraction

An X-ray diffraction study of the pure drug, biopolymers and their preparations was conducted using a D8 Discover (Bruker, Germany) to assess the effect of the dispersion techniques on the crystallinity of the drug. The scanning of samples was done in the 8–70° diffraction angle range under the following conditions: Cu-K_{∞} radiation 1.5406 A° (source), 4°/min scan speed, scintillation detector, primary slit 1 mm, secondary slit 0.6 mm.

Tablet Hardness Testing

Tablet hardness was tested (in terms of force applied to break) using a tablet hardness machine (Curio, Pakistan).

Solubility Equilibrium

For equilibrium solubility studies, an excess quantity of the prepared formulations was added to a vial containing 5 ml of water at 37°C and 25°C. The vial was placed in a shaker at 37°C and 25°C at 100 rpm with a controlled room temperature. After seven days, the sample was filtered through a 0.45 μm millipore filter (Acrodisc GF syringe filter, Pall Life Sciences, USA) and 1 ml of each solution was diluted to 10 ml with distilled water. Diluted samples were assayed spectrophotometerically at 290 nm using a Shimadzu 1600 UV-Visible spectrophotometer (Shimadzu, Japan). In solvent comparison studies, a control experiment was performed on ARMN without PVP to confirm any degradation in various solvents.

Results and Discussion

Artemisinin-PVP and -PEG solid dispersions were formulated at ratios of 1 : 9, 2 : 8, 3 : 7, 5 : 5 and 6 : 4 for drug: PVP K30, drug:PVP K30 and K25, drug:PVP K30 and PEG6000 and drug:PVP K30 and PEG4000.

Drug Content

The ARMN content in all preparations was determined by UV analysis. The drug contents ranged between 95.8% and 99.5% of the theoretical values.

Dissolution Studies

The calibration curve for pure artemisinin was prepared using methanol as the solvent due to poor solubility in water (Figs. 1, 2). The curve shows linear (coefficient of determination = R^2 = = 0.9991, Y-equation Y = 0.0503X + 0.0308) behavior between artemisinin concentration and UV absorbance. The concentration of artemisinin in physical mixtures and solid dispersions were calculated using a standard curve. The ultimate pharmaceutical performance of different solid dispersions was investigated by determining their dissolution profile. Dissolution study sampling was done at 0, 10, 20, 30, 40, 60, 120, 180, 240, 300, 360, 480 and 600 minutes.

The dissolution profiles of physical mixtures, solid dispersions and lyophilized solid dispersions in all formulations exhibited an improvement in the dissolution behavior of formulated artemisinin as compared to pure artemisinin. The lyophilized solid dispersions showed the highest dissolution among all the formulations. The order of decrease in dissolution rate was LYO > SD > PM > Pure ARMN. This may be due to physical interaction between drug and carrier.

According to the dissolution study, drug releases from physical mixtures were higher than from the pure drug. Solid dispersions exhibited a better dissolution rate than physical mixtures due to the increase in drug wetability. Overall, the drug release of the formulations made by the lyophilization method delivered high drug release followed by solid dispersion, physical mixture and pure drug, in that order. When drug release was compared among formulations with pure biopolymers and mixtures of biopolymers, it was found that the drug release pattern of solid dispersions of ARMN : PVP K30 offered better drug release than solid dispersions of ARMN: PVP K25 and K30, ARMN : PVP K30 and PEG4000 and PVP K30 and PEG6000. This means that PVP K30 is the best drug carrier as compared to mixtures of biopolymers. When drug release was compared among mixtures of biopolymers, ARMN: PVP K25 and K30 showed better drug release, followed by ARMN: PVPK30 and PEG4000 and PVPK30 and PEG6000, in that order.

FTIR Spectra

The FTIR spectra of pure artemisinin showed characteristic bands at 3379 cm^{-1} (O-H stretching vibrations), 2947 cm^{-1} (Fermi resonance of the symmetric CH_3 stretch with overtones of the methyl bending modes), 1093 cm^{-1} (C-O stretching), 876 cm^{-1} (O-O-C stretching in boat/twist form) and 825 cm^{-1} (O-O stretching in boat/twist form). It indicates the properties of the O-O-C component, respectively representing the 1,2,4-trioxane ring.

The FTIR spectra of pure PEG4000 exhibited characteristic peaks indicating the specific mode of the molecules. The characteristics signals were at 3427 cm^{-1}(N-H stretching), 2887 cm^{-1}(C-H stretching vibration), 1643 cm^{-1}(C = C Stretching) and 1281 cm^{-1}(C-N stretching vibrations).

The FTIR spectra of pure PVP K25 exhibited characteristic peaks associated with specific structural characteristics of the molecules. The spectrum of pure PVP K25 presented characteristics signals at 3444 cm^{-1} (O-H stretching vibrations), 2924 cm^{-1} (C-H stretching vibrations), 1659 cm^{-1} (C = O Carbonyl stretching), 1374 cm^{-1} (C-H bending) and 1290 cm^{-1} (C-N stretching vibrations).

The FTIR spectra of artemisinin and its formulations with PEG4000, PEG6000, PVP K25 and PVP K30 are presented in Figures 3–7. The FTIR

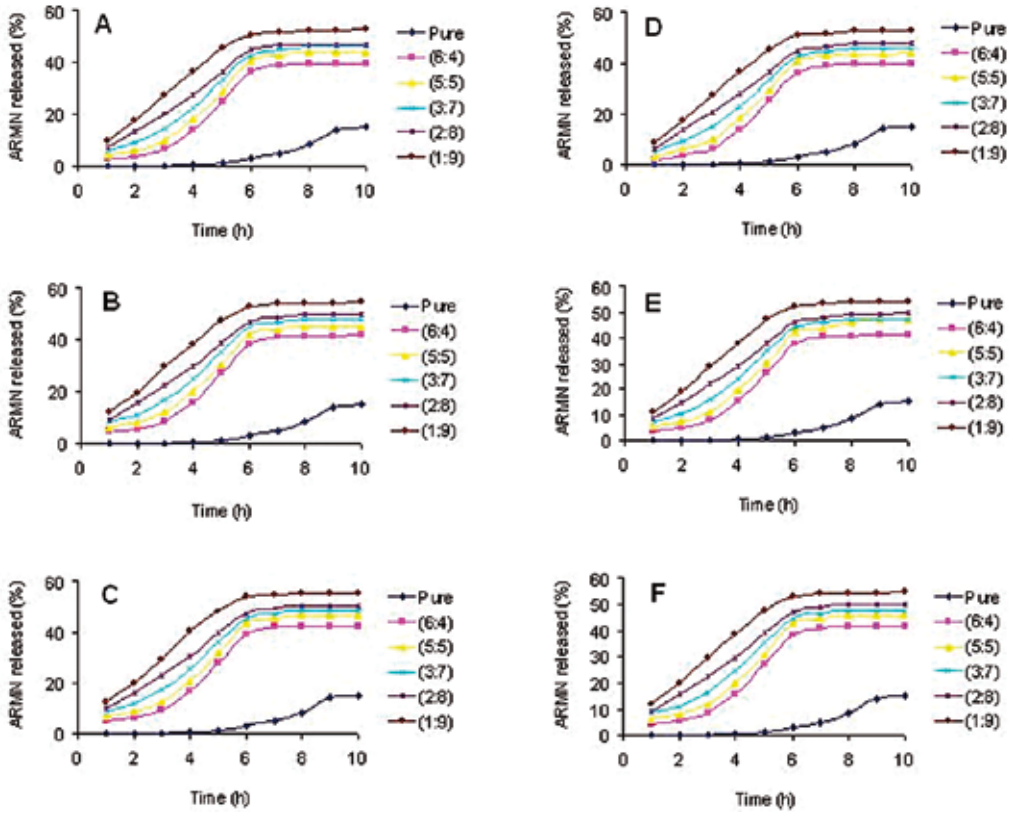

Fig. 1. The effect of PVP K30 (A, B, C) and PVP K25+K30 (D, E, F) contents and the method of preparation on dissolution behavior (A and D = physical mixtures; B and E = solid dispersions; C and F = lyophilized dispersions)

Ryc. 1. Wpływ zawartości PVP K30 (A, B, C) i PVP K25 + K30 (D, E, F) i sposobu przygotowania na rozpuszczalność. (A i D = mieszaniny fizyczne, B i E = stałe dyspersje, C i F = liofilizowane dyspersje)

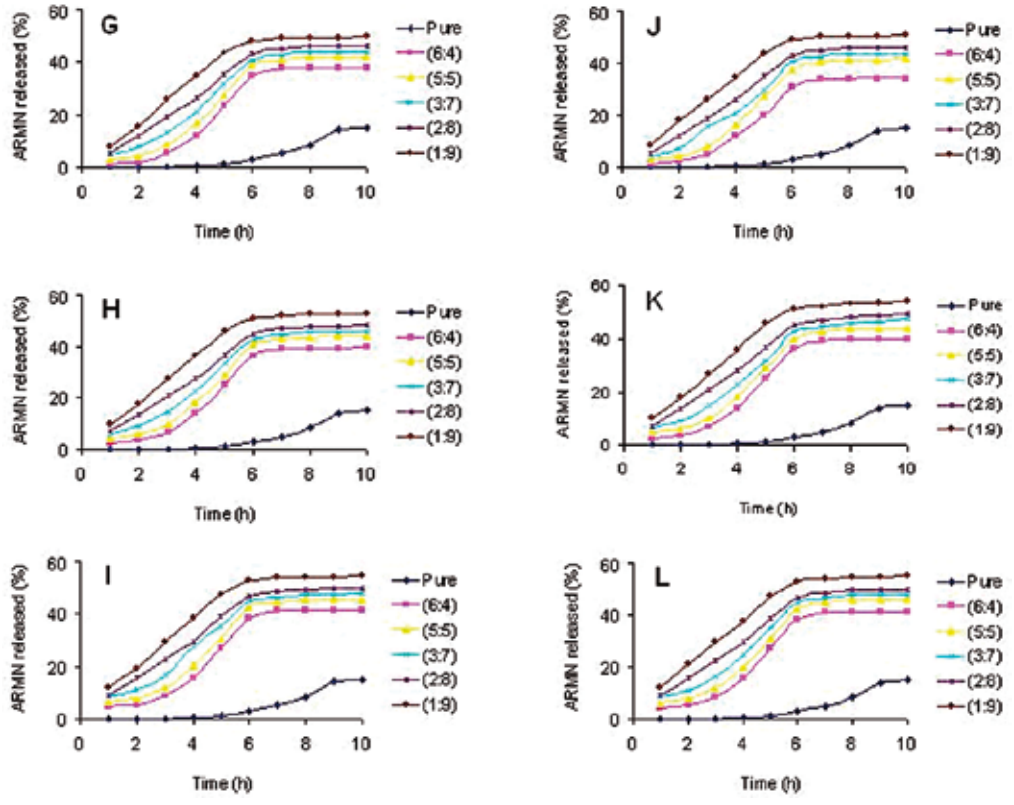

Fig. 2. The effect of PVP K30+PEG6000 (G, H, I) and PVP K25+PEG4000 (J, K, L) contents and the method of preparation on dissolution behavior (G and J = physical mixtures; H and K = solid dispersion; I and L = lyophilized dispersions)

Ryc. 2. Wpływ zawartości PVP K30 + PEG6000 (G, H, I) i PVP K25 + PEG4000 (J, K, L) i sposobu przygotowania na rozpuszczalność. (G i J = mieszaniny fizyczne, H i K = stałe dyspersje, I i L = liofilizowane dyspersje)

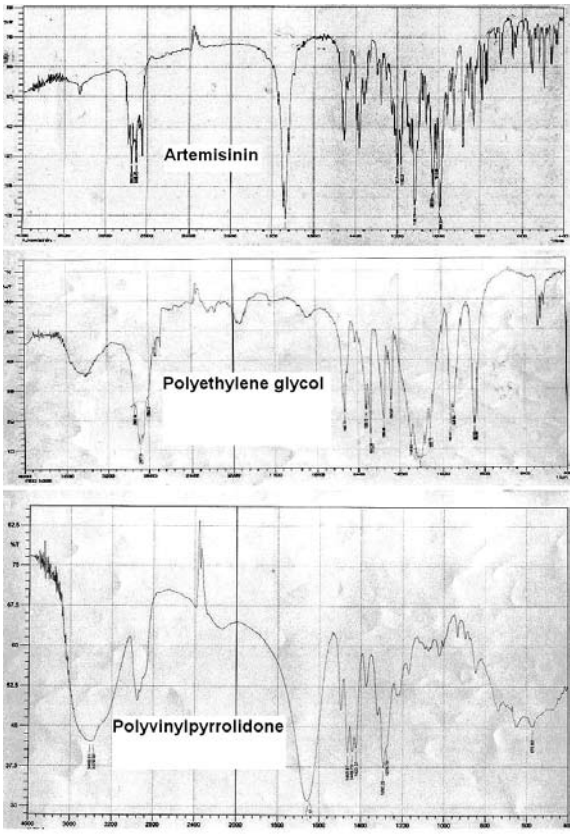

Fig. 3. The FTIR spectra of pure constituents

Ryc. 3. Widma FTIR czystych składników

analysis indicated a difference in intermolecular hydrogen bonding interaction at N-H or O-H between ARMN: PVP and PEG among solid dispersions. The FTIR spectra of the solid dispersions showed that the interaction of artemisinin in PVP and PEG was enhanced with an increase in polymer content, with the maximum in SDs of PVP K30 at the ratio of 1 : 9. The presence of N-H and C = O peaks in addition to artemisinin peaks in the spectra of solid dispersions indicated a stronger interaction between the drug and the carrier. The shifting of O-H and C-H stretching vibrations in FTIR spectra revealed red shifting and blue shifting of the carbonyl group in the fingerprint region, indicating interaction among artemisinin and the biopolymers. The extent of the interaction varied depending on the nature and molecular weight of the carriers and on the drug-carrier ratio. As the ratio of the biopolymer (PVP and PEG) to the drug (ARMN) increased, this indicated that high biopolymer binding to the drug improves the pharmaceutical quality.

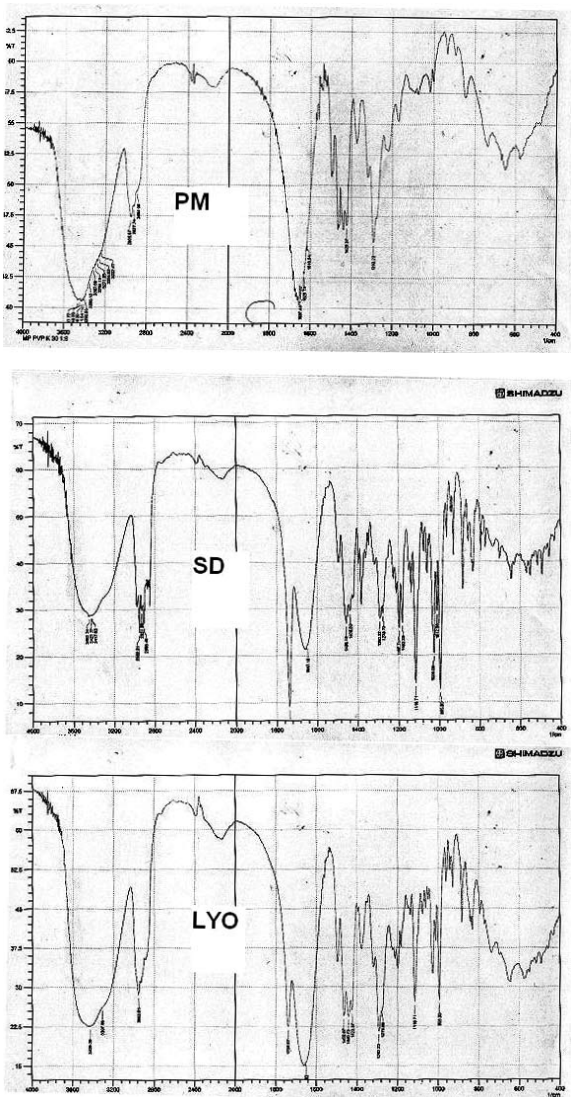

Fig. 4. FTIR spectra of a physical mixture (PM), solid dispersion (SD) and lyophilized solid dispersion (LYO) of ARMN-PVP K30 at a 1 : 9 ratio

Ryc. 4. Widma FTIR mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 w stosunku 1 : 9

X-ray Diffraction

An X-ray diffraction study of the pure drug, biopolymers and their preparations was conducted using a D8 Discover (Bruker, Germany) to assess the effect of the dispersion techniques on the crystallinity of the drug. The XRD patterns (Figs. 8–11) revealed that phase transitions of artemisinin took place when PVP and PEG were mixed with artemisinin. The intensity and number of peaks representing a crystalline structure were reduced as the polymer content increased. The maximum decrease was in solid dispersions of PVPK30 at a drug:carrier ratio of 1 : 9, followed by the mixture of PVPK30 and K25 (1 : 9), PVP K30 and PEG6000 (1:9) and PVPK30 and

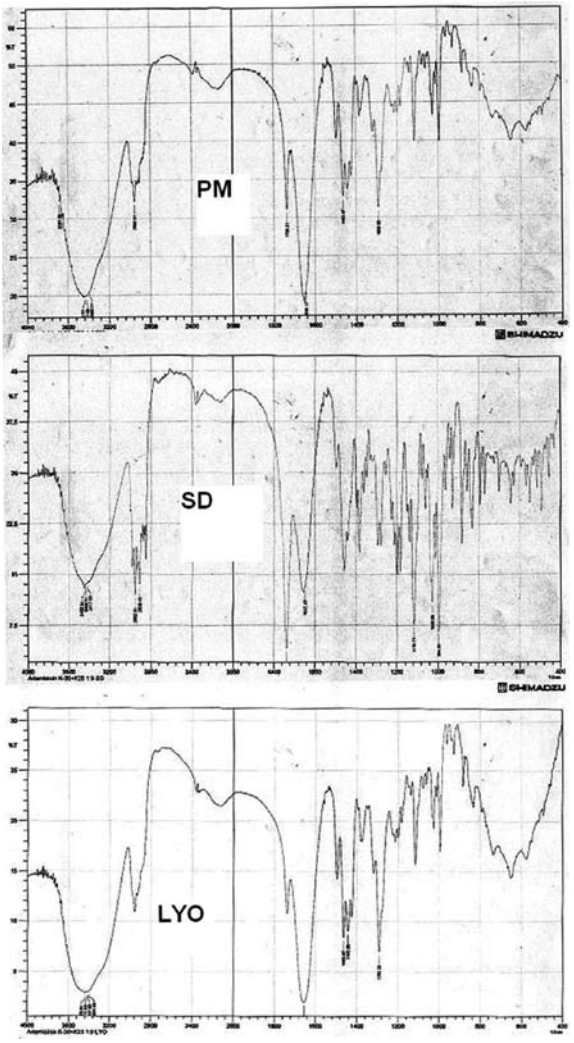

Fig. 5. FTIR spectra of a physical mixture (PM), solid dispersion (SD) and lyophilized solid dispersion (LYO) of ARMN-PVP K25 and K30 at a 1 : 9 ratio

Ryc. 5. Widma FTIR mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K25 w stosunku 1 : 9

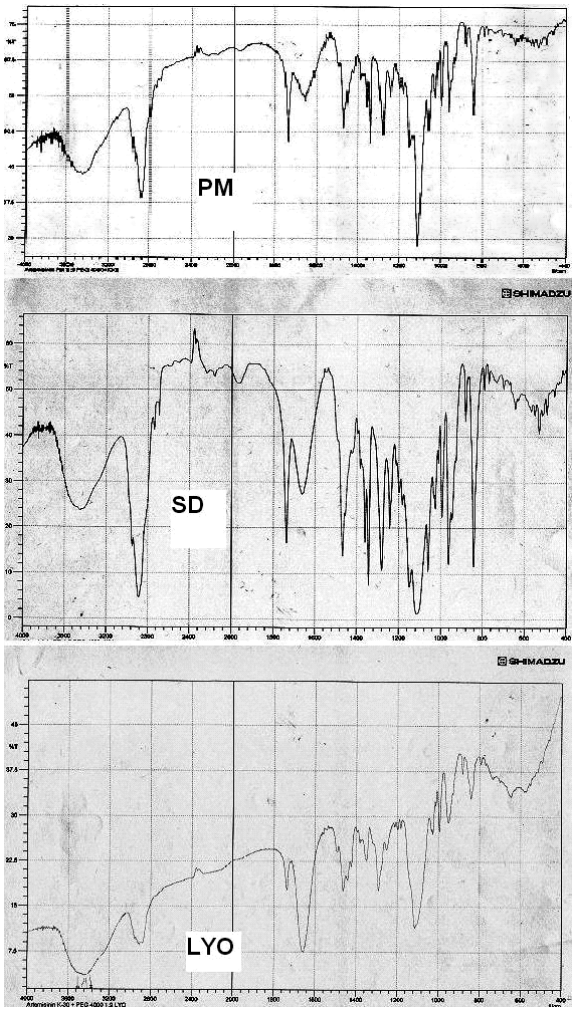

Fig. 6. FTIR spectra of a physical mixture (PM), solid dispersion (SD) and lyophilized solid dispersion (LYO) of ARMN-PVP K30 and PEG4000 at a 1 : 9 ratio

Ryc. 6. Widma FTIR mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 i PEG4000 w stosunku 1 : 9

PEG4000 (1 : 9). The extent of the interaction varied depending on the nature and molecular weight of the carriers and on the drug-carrier ratio. As the ratio of biopolymer (PVP and PEG) to the drug (ARMN) increased, this indicated that high biopolymer binding to the drug improves the pharmaceutical quality.

Solubility in Equilibrium Studies at 37°C

Pure Artemisinin

Artemisinin was found to be poorly soluble in water after seven days of shaking in deionized water at 37°C. Pure artemisinin was 1.04 μg/ml soluble in water at 37°C.

Artemisinin-PVP K30 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 5.642 to 13.147 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentrations of artemisinin in water as compared to physical mixtures, i.e. 6.593–15.974 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 7.933–17.245 μg/ml.

Artemisinin-PVP K30 and K25 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the prepara-

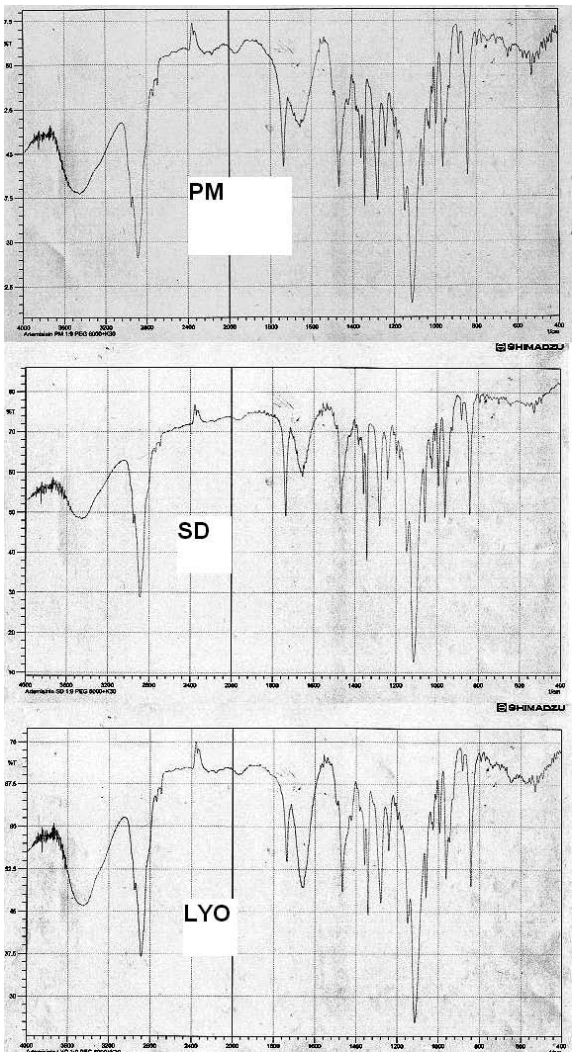

Fig. 7. FTIR spectra of a physical mixture (PM), solid dispersion (SD) and lyophilized solid dispersion (LYO) of ARMN-PVP K30 and PEG6000 at a 1 : 9 ratio

Ryc. 7. Widma FTIR mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 i PEG4000 w stosunku 1 : 9

tions. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 4.559 to 11.444 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentrations of artemisinin in water as compared to physical mixtures, i.e. 5.097–12.985 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 6.025–14.833 μg/ml.

Artemisinin-PVP K30 and PEG4000 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 3.927 to 9.966 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentration of artemisinin in water as compared to physical mixtures, i.e. 4.391–11.795 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 5.027–13.632 μg/ml.

Artemisinin-PVP K30 and PEG6000 Preparations

Lyophilized solid dispersions released highest amount of artemisinin as compared to all other preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 4.533 to12.413 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentration of artemisinin in water as compared to physical mixtures, i.e. 5.615–14.534 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 6.318–16.162 μg/ml.

Solubility in Equilibrium Studies at 25°C

Pure Artemisinin

Artemisinin was found to be poorly soluble in water after seven days of shaking in deionized water at 25°C. Pure artemisinin was 0.97 μg/ml soluble in water at 25°C.

Artemisinin-PVP K30 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 5.678 to 13.602 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentrations of artemisinin in water as compared to physical mixtures, i.e. 6.517–16.434 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 6.663–17.453 μg/ml.

Artemisinin-PVP K30 and K25 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 4.916 to 11.692 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentrations of artemisinin in water as compared to physical mixtures, i.e. 5.013–13.108 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 5.623–14.856 μg/ml.

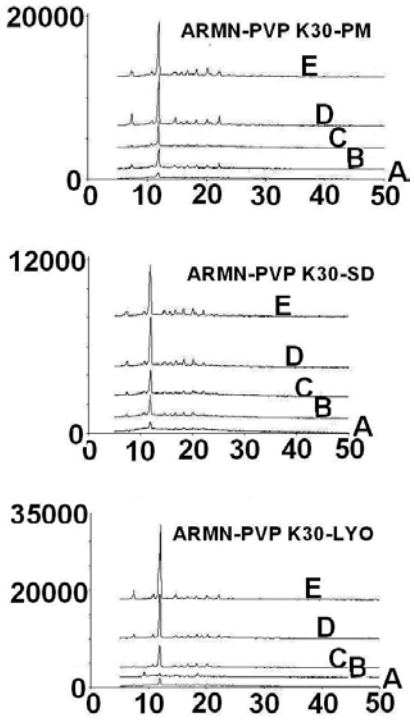

Fig. 8. X-ray diffraction patterns of physical mixtures (PM), solid dispersions (SD) and lyophilized solid dispersions (LYO) of ARMN-PVP K30 at ratios of 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) and 6 : 4 (E)

Ryc. 8. Widma dyfrakcji rentgenowskiej mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 w stosunku 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) i 6 : 4 (E)

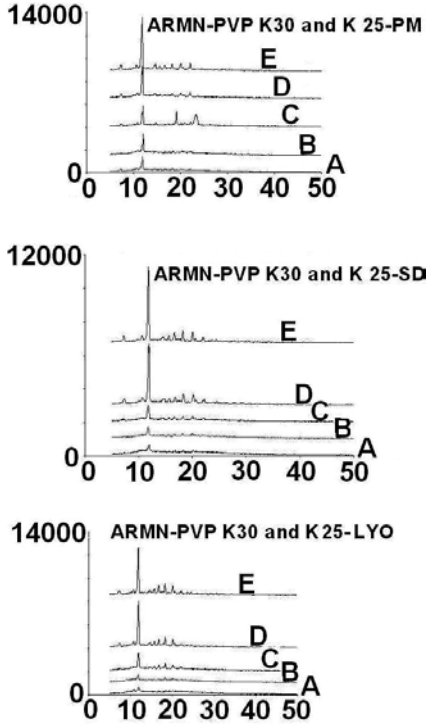

Fig. 9. X-ray diffraction patterns of physical mixtures (PM), solid dispersions (SD) and lyophilized solid dispersions (LYO) of ARMN-PVP K30 and K25 at ratios of 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) and 6 : 4 (E)

Ryc. 9. Widma dyfrakcji rentgenowskiej mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 i K25 w stosunku 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) i 6 : 4 (E)

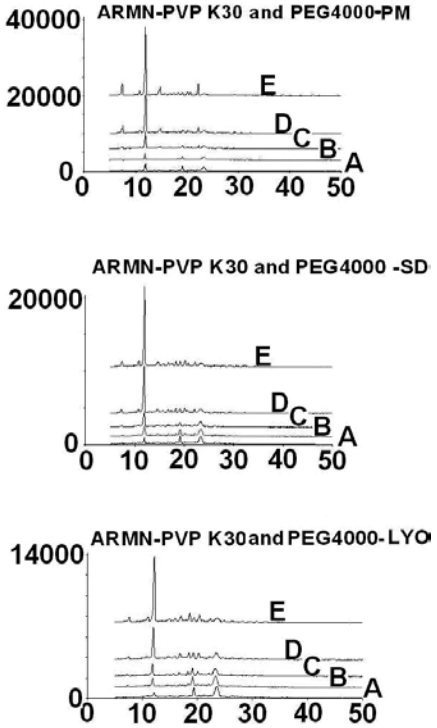

Fig. 10. X-ray diffraction patterns of physical mixtures (PM), solid dispersions (SD) and lyophilized solid dispersions (LYO) of ARMN-PVP K30 and PEG4000 at ratios of 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) and 6 : 4 (E)

Ryc. 10. Widma dyfrakcji rentgenowskiej mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 i PEG4000 w stosunku 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) i 6 : 4 (E)

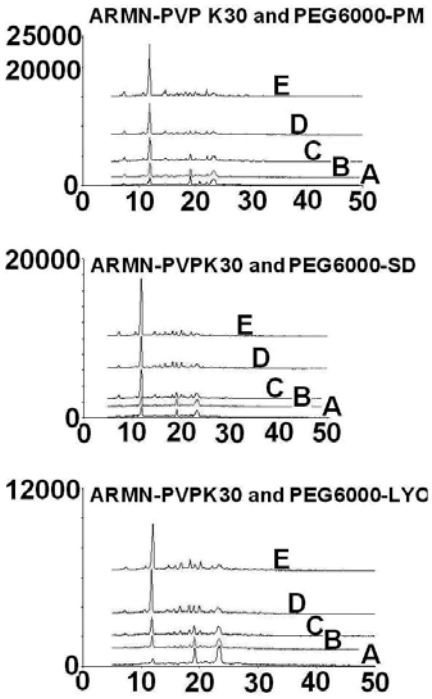

Fig. 11. X-ray diffraction patterns of physical mixtures (PM), solid dispersions (SD) and lyophilized solid dispersions (LYO) of ARMN-PVP K30 and PEG6000 at ratios of 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) and 6 : 4 (E)

Ryc. 11. Widma dyfrakcji rentgenowskiej mieszaniny fizycznej (PM), stałej dyspersji (SD) i liofilizowanej stałej dyspersji (LYO) z ARMN-PVP K30 i PEG6000 w stosunku 1 : 9 (A), 2 : 8 (B), 3 : 7 (C), 5 : 5 (D) i 6 : 4 (E)

Artemisinin-PVP K30 and PEG4000 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 3.792 to11.962 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentration of artemisinin in water as compared to physical mixtures, i.e. 5.103–13.814 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 6.015–15.374 μg/ml.

Artemisinin-PVP K30 and PEG6000 Preparations

Lyophilized solid dispersions released the highest amount of artemisinin among all the preparations. Physical mixtures of artemisinin showed enhanced solubility with an increase in PVP content from 4.854 to12.17 μg/ml (from a ratio of 6 : 4 to 1 : 9). Solid dispersions released comparatively higher concentration of artemisinin in water as compared to physical mixtures, i.e. 5.207–14.534 μg/ml. Lyophilized solid dispersions showed the highest solubility, i.e. 5.831–15.041 μg/ml.

Equilibrium solubility was enhanced with increases in polymer content in all samples. Lyophilized solid dispersions (ARMN-PVPK30) showed the highest solubility in water, followed by solid dispersions and physical mixtures, in that order.

The authors concluded basing on this work that the rate of artemisinin dissolution can be increased substantially by formulating it as a solid dispersion in PVP K30 using the lyophilization method. The addition of superdisintegrants such as PEG to the solid dispersions played an important role in the enhancement of the dissolution rate. This study has also paved the way for the formulation of fast-dissolving tablets of artemisinin using the lyophilization dispersion method.

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