DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF SOLID DISPERSIONS OF ARTEMETHER AND LUMEFANTRINE BY SOLVENT EVAPORATION METHOD USING HYDROPHILIC POLYMERS

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INTRODUCTION

Malaria has been described since ancient times as a seasonal periodic fever. The name malaria is originated from Latin’s mal aire which means bad air. Malaria is characterized by fever, headache, muscle ache, back pain, joint pains, chest pain, nausea, sometimes vomiting and coughs, in severe cases it leads to coma and finally it causes death of the persons approximately one million people every year [1]. Malaria is mainly spread in Sub-Saharan Africa, mainly among children under five years of age and pregnant women are more prone to malaria. Artemether and Lumefantrine are used to treat uncomplicated malaria caused by P. falciparum in a fixed ratio dosage of 1:6.

Among all drug delivery systems, oral delivery is the most convenient and commonly employed route of drug delivery because it possesses many advantages compared to other routes of drug delivery systems. Easy administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design are the major advantages of this dosage form [2]. At present, the upcoming new chemical entities (NCE) are developed as a solid dosage form for oral administration. But more than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water.

These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. This poor oral bioavailability of the drug is the major challenging task for the designing the oral dosage forms. The poor oral bioavailability of the drug is due to low solubility, low dissolution of the drug rather than permeation of the drug through epithelia of gastrointestinal tract. Hence permeability, solubility and dissolution of a drug play an important role in determining the bioavailability of a drug when administered orally.

In order to increase bioavailability, solubility of a drug should be increased. There are various techniques to increase solubility of a drug like solid dispersion (solvent evaporation method, fusion process, melt-mixing freeze-dried, fusion-solvent method, kneading technique and co-preparation), spherical agglomeration and evaporative precipitation in aqueous solution, pro drug approach, polymorphism, complexation, pH adjustment, co-solvents, use of surfactant and particle size reduction [3]. Amongst all techniques solid dispersion is more effective in technique.

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, in 1961. They developed practical method and achieved success in improving the bioavailability of poorly water soluble drugs by using the hydrophilic carriers [4]. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers in the preparation of solid dispersions polyvinylpyrrolidone (Povidone, PVP) [5, 6], polyethylene glycols (PEG 6000) [7], Surfactants like Tween-80, Poloxamer, and Sodium Lauryl Sulphate (SLS). The main mechanism involved in the solid dispersion is reduction of the particle size, Drug in amorphous state, Particles with high porosity, Particles with improved wettability, solubilization of the drug by the carrier at the diffusion layer. It has been suggested by many authors that the solubility of low aqueous soluble drugs was increased by incorporating surfactants in the dissolution medium like sodium lauryl sulphate, Tween~80, benzalkonium chloride (BKC), cetrimide etc.

Artemether and Lumefantrine are highly lipophilic drugs and are poorly soluble in water with bioavailability of 1.18ug/ml and 0.44ug/ml respectively. Artemether has rapid onset of action and is rapidly eliminated from the body. It is thus thought to provide rapid symptomatic relief by reducing the number of malarial parasites whereas Lumefantrine has a much longer action and is used to clear residual parasites [8]. In April 2002, FDC included this first fixed dose combination of drugs into model list of essential drugs [9,10].

According to WHO this combination drugs can be given as a first line treatment for uncomplicated malaria. The treatment by using these drugs is a Radical treatment (Treatment given for 3 days). Both the drugs belongs to BCS class IV having low solubility and low permeation so it is necessary to increase the solubility of the drugs.
in order to increase the bioavailability of the drugs to show its pharmacological action. In the present study an attempt was made to enhance the solubility of Artemether and Lumefantrine by Solid dispersion (solvent evaporation) method using PVP K-30, and POLOXAMER were used as carriers.

**MATERIALS AND METHODS**

**Materials**

Artemether and Lumefantrine were obtained as a gift sample from Mylan, Hyderabad, Andhra Pradesh, India, PEG 6000, PVP K-30 and POLOXAMER were obtained from Central drug house, New Delhi, India. All solvents and chemicals were used of analytical grade and were obtained from S.D. Fine-Chem Ltd, Mumbai, India.

**Methods**

Preparation of solid dispersions by solvent evaporation method

**Method A**

In case of single polymer solid dispersion, the drug and the polymer was dissolved in adequate quantity of solvent (Acetone in case of Artemether and Chloroform in case of Lumefantrine) and stirred continuously for about 30min at room temperature to obtain a clear solution. To this solution, 10mg of aerosil was added and stirred at room temperature until two thirds of the solvent has evaporated. The stirring was stopped and the balance solvent was removed by drying under vacuum at room temperature [11, 12].

**Method B**

In case of solid dispersion containing a combination of PEG 6000 and PVP K-30, the former was first melted with the aid of heat and the later was added along with the drug solution [13]. The rest of the preparation of solid dispersion was same as method A. The dried powder was collected and passed through mesh no.60 and stored for further use.

<table>
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<th>Carrier</th>
<th>Drug: Polymer</th>
<th>Drug (mg)</th>
<th>Polymer (mg)</th>
<th>Aerosil (mg)</th>
<th>Acetone (ml)</th>
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<th>Polymer (mg)</th>
<th>Aerosil (mg)</th>
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**Evaluation parameters**

**FT-IR studies** [14]

FT-IR was performed for pure drug, blank (only Excipient without drug) and optimized Solid dispersion were obtained on FTIR (Perkin Elmer spectrum one, UK) Spectrophotometer.

Samples (About 3 mg of sample and 100 mg of potassium bromide) were mixed, compressed into pellets and transmittance was measured from wave number 450 to 4000 cm\(^{-1}\) using FT-IR spectrophotometer (FTIR –T2154, Perkin Elmer, UK)

**XRD studies** [15]

The scattering of X-rays from atoms produces a diffraction pattern, which contains information about the atomic arrangement within the crystal. The crystallinity of pure drug, Blank (only excipients) and optimized solid dispersion was assessed by X ray diffraction studies (Bruker D-8 advance Germany). XRD Studies were performed on the samples by exposing them to anode Cu and scanned from 2.000° to 65.005°, 20 at a step size of 0.013° and step time of 13.6s.

**Preliminary Solubility Studies of Artemether and Lumefantrine**

An excess quantity of drugs was placed in 20 ml capacity conical flasks containing accurately measured 10 ml of different solvents like distilled water (P\(^{n}\) 7.0), P\(^{n}\) 1.2, 0.1N HCl and phosphate buffer at P\(^{n}\) 7.2 separately. The contents of the test tubes were sonicated for 20 min at room temperature in an ultrasonic bath (Bandelin sonorex). Then these test tubes were wrapped with Aluminum foil at their open end, and kept for shaking at 75rpm for 30 hrs at 25±0.5°C in a mechanical shaker. The test-tubes were centrifuged for 20min at 1000rpm and superant solution was collected and filtered using What’s man filter paper. The filtrate was analyzed using spectrophotometrically (UV-1800 Shimadzu) at a \(\lambda_{\text{max}}\) of 211nm for Artemether and 342nm for Lumefantrine after suitable dilutions. The amount of drugs dissolved in various solvents was estimated.

**Solubility Study** [16]

In case of solubility study all the parameters of preliminary solubility were kept same except along with the excess amount of drug, prepared solid dispersions were also studied and instead of different solvents, only distilled water(P\(^{n}\) 7.0) was used as solvent for both Artemether and Lumefantrine.

The filtrate was analyzed using spectrophotometrically (UV-1800 Shimadzu) at a \(\lambda_{\text{max}}\) of 211nm for Artemether and 342nm for Lumefantrine after suitable dilutions. The amount of drugs dissolved by using various carriers was estimated by comparing with the pure drug solubility.

**In Vitro Dissolution Studies** [17, 18]

In vitro dissolution studies of solid dispersion of Artemether was carried out using USP type II dissolution testing apparatus (paddle type, TDL-08L, Electrolib, Mumbai, India) in 900ml of P\(^{n}\) 7.2 Phosphate buffer maintained at 37±0.5°C stirred at 50 rpm. 0.5% SLS was used to create sink condition.

In case of Lumefantrine all the parameters were kept same except the dissolution medium being used was P\(^{n}\) 1.2, 0.1N HCl and Tween 80 was used to create sink condition. An aliquot of 5ml Samples were withdrawn at specific time intervals, replacing the same amount with the fresh medium in order to keep the total volume constant.

The samples were analyzed using spectrophotometrically (UV-1800 Shimadzu) at a \(\lambda_{\text{max}}\) of 211nm for Artemether and 342nm for Lumefantrine after suitable dilutions.
RESULTS AND DISCUSSION

FTIR studies

FTIR studies were carried out for the pure drug – Artemether, formulation SDAF5 and their spectra are as shown in Figure.1 & Figure. 2. The characteristic peaks of the pure drug – Artemether was assigned from standard literature. These included O-H stretching, C-H stretching and C-H bending as shown below.

1. 3462.34 cm⁻¹: O-H stretching
2. 2937.48 cm⁻¹: C-H stretching
3. 1433.51 cm⁻¹: C-H bending

As seen in figure 1, the spectra for Artemether exhibits a broad peak at 3462.34 cm⁻¹ due to alcohols and phenols (O-H) stretching vibration, 2956.97 cm⁻¹ due to alkanes (C-H) stretching vibration, 1433.51 cm⁻¹ due to alkanes (C-H) bending vibration.

Fig. 1: it shows ftir spectra of pure drug of artemether

The FTIR results from optimized formulation SDRF5 exhibited broad peaks at 3351.85 cm⁻¹ due to alcohols and phenols (O-H), 2889.01 cm⁻¹ due to alkanes (C-H) stretching vibration, 1343.33 cm⁻¹ due to alkanes (C-H) bending vibration.

The intensity and position of these characteristic peaks permits easy interpretation of any possible interaction between the drug and the excipients in the formulation. The results clearly showed that there was no interaction between the drug and the excipients in the prepared formulation SDAF5. The drug - Artemether was intact and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into pellets.

Fig. 2: it shows ftir spectra of solid dispersed artemether in case of lumefantrine

FTIR studies were carried out for the pure drug – Lumefantrine, formulation SDAR5 and their spectra are as shown in Figure. 3 & Figure. 4. The characteristic peaks of the pure drug – Artemether was assigned from standard literature. These included O-H stretching, C-H stretching and C-H bending as shown below.

1. 3394.72 cm⁻¹: O-H stretching
2. 2951.82 cm⁻¹: C-H stretching
3. 1442.13 cm⁻¹: C-H bending

As seen in Figure. 3, the spectra for Artemether exhibits a broad peak at 3394.72 cm⁻¹ due to alcohols and phenols (O-H) stretching vibration, 2951.82 cm⁻¹ due to alkanes (C-H) stretching vibration, 1442.13 cm⁻¹ due to alkanes (C-H) bending vibration.

Fig. 3: it shows ftir spectra of pure drug of lumefantrine

The FTIR results from optimized formulation SDRF5 exhibited broad peaks at 3272.65 cm⁻¹ due to alcohols and phenols (O-H), 2887.59 cm⁻¹ due to alkanes (C-H) stretching vibration, 1326.07 cm⁻¹ due to alkanes (C-H) bending vibration.

Fig. 4: it shows ftir spectra of solid dispersed lumefantrine

The results clearly showed that there was no interaction between the drug and the excipients in the prepared formulation SDRF5. The drug Lumefantrine was intact and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into pellets.

XRD studies

The diffraction spectrum of pure Artemether showed that the drug was crystalline as demonstrated by numerous peaks observed at 2θ of 9.29°, 8.76°, 7.87°, 6.14°, 5.44°, 4.69°, 3.92°, 2.62° and 2.50° etc were shown in Figure.5. The extent of dissolution will depend upon crystallinity of the drug.

The amorphous or metastable form will dissolve at the fastest rate because of its higher internal energy and greater molecular motion, which enhance the thermodynamic properties compared to crystalline materials. In the solid dispersion of Artemether showed same peaks of Pure Artemether are seen but with decreased intensity, were shown in Figure. 6. The decreased intensity of peaks is due to presence Melted PEG 6000 and PVP K-30 followed by
solvent evaporation method for preparation of solid dispersion. From the PXRD result we can conclude that the crystalline nature of the drug was converted into micro crystalline nature (partially crystalline nature). Even the micro crystalline nature is obtained there will not be any sign chemical reaction between drug and polymers used in the formulation. This was practically proven by Valkadren et al., characterized Indomethacin–PEG 6000 SDs prepared by melting method and concluded that the drug was in microcrystalline form and no chemical interaction took place between Indomethacin and PEG 6000 either in solution or in the solid state. The present finding i.e. the presence of microcrystalline or partially crystalline state of Artemether in SDs is in agreement with several studies on other drugs [19]. In case of Lumefantrine, the diffraction spectrum of pure Lumefantrine showed the drug was crystalline in nature as demonstrated by numerous peaks observed at 2θ of 16.59°, 12.53°, 6.78°, 5.94°, 4.96°, 4.68°, 3.83°, 3.68°, 2.27° and 2.49° etc were shown in Figure 7. The spectrum of solid dispersed Lumefantrine showed same peaks of pure Lumefantrine but with decreased frequency were shown in Figure 8, remaining process kept same as that of Artemether and solid dispersed Artemether PXRD report.

**Solubility Study**

Solubility of Artemether increased by 33.22 times in case of PVP K-30 (39.20ug/ml) compared to POLYXAMER (28.81times, 28.10ug/ml) and PEG 6000 (26.71times, 31.52ug/ml). When a combination of carriers of PVP K-30 and PEG 6000 was used, there was further increase in solubility of Artemether and the solubility increased by 50.72times (59.85ug/ml) in case of solid dispersion SD5 which contains 3:2 ratio of PVP K-30 and PEG 6000 were shown in Figure 9.

In case of Lumefantrine solubility increased by 33.45 times in case of PVP K-30 (11.76ug/ml) compared to POLYXAMER (25.22times, 11.10ug/ml) and PEG 6000 (26.72times, 11.76ug/ml). When a combination of carriers of PVP K-30 and PEG 6000 was used, there was further increase in solubility of Artemether and the solubility increased by 67.38times (29.65ug/ml) in case of solid dispersion SD5 which contains 3:2 ratio of PVP K-30 and PEG 6000 were shown in Figure 10.

**In Vitro Dissolution Studies**

In vitro dissolution studies of solid dispersions and pure Artemether was carried in pH 7.2 Phosphate buffer and 0.5%SLS. The results reveals that the increased percentage drug release was shown by all for Solid dispersion formulations compared to pure drug. The
percentage drug released from solid dispersion formulations containing single polymer SDA1-SDA3 at the end of 60th minute was 58.66%, 63.56% and 70.59% only. But in case of solid dispersion containing combination of PVP K-30 and PEG 6000 in 2:3 and 3:2 ratio showed increased dissolution rate is seen compared to single polymer formulation. Optimized formulation SDA5, containing PVP K-30 and PEG 6000 in the ratio of 3:2 released 97.81% drug at the end of 60th minute. This increased percentage of drug released from formulation SDA5 is more compared to pure Artemether i.e. 24.21% drug released at the end of 60th minute from Artemether. The dissolution profiles of all the formulations and pure Artemether are shown in Figure 11.

This increased dissolution rate of formulations of Artemether and Lumefantrine may be due to the effect of two hydrophilic polymers used in the formulations where the solubilization effect of PVP K-30 in increasing dissolution rate is it inhibits crystallinity of drug, reduction of particle aggregation of the drug, produces porous nature to the solid dispersion and the solubilization effect of PEG 6000 is it reduction of particle aggregation of the drug formation of microcrystalline or amorphous drug, increased wettability and dispersibility, and alteration of the surface properties of the drug particles.

CONCLUSION

The solubility and dissolution rate of Artemether and Lumefantrine was increased by solid dispersion prepared by solvent evaporation technique by using Hydrophilic polymers PVP K-30, PEG 6000, POLYOXAMER. From the dissolution studies the optimized formulations containing combination polymers in 3:2 showed increased dissolution rate. The increased solubility and dissolution rate of Artemether and Lumefantrine from the solid dispersion may be due to the solubilization effect of PEG 6000 and PVP K-30, PEG 6000 reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility and alteration of the surface properties of the drug particles whereas PVP K-30 inhibited the crystallization of drug, resulting in the amorphous state form of the drug in solid dispersion. PXRD results conforms the decreased crystalline nature of the drug in solid dispersion. From the FTIR studies it indicates there is no sign of incompatibility between the drug and polymers used in the solid dispersion. From the above studies it can be concluded that solid dispersion prepared by using 3:2 ratio of PVP K-30 and PEG 6000 showed better dissolution than other formulations, hence this solid dispersion prepared by combination of polymers can be used to enhance the bioavailability of Artemether and Lumefantrine.

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