Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6 Issue 2, 2014

Research Article

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

ANNA BALAJI[1], HARISHA KUMARI M[1]*, UDAY KUMAR G.[2]

[1]Center for Biopharmaceutics and Pharmacokinetics, Trinity College of Pharmaceutical Sciences, Peddapally, Karimnagar 505 172. Andhra Pradesh, India. Email: harishakumari95@gmail.com

Received: 04 Jan 2014, Revised and Accepted: 21 Feb 2014

ABSTRACT

Objective: To prepare a chemically stable solid dispersion to increase the drug solubility and to improve its dissolution rate by using hydrophilic polymers.

Methods: Solid dispersion of Artemether and Lumefantrine are prepared by using hydrophilic polymers (PVP K-30, PEG 6000 and POLOXAMER) in single and in combinations ratios by solvent evaporation method.

Results: The prepared solid dispersions were evaluated for their compatibility study by FTIR studies, crystalline nature by PXRD, solubility studies and *in vitro* dissolution studies. FTIR results indicated that there was no incompatibility between the drug and the polymers; PXRD results indicate there is decreased in crystalline nature of the drugs. *In vitro* dissolution study reveals that solubility of the drug is increased in all solid dispersion formulations compare to pure drugs, *In vitro* dissolution study of optimized formulation of Artemether (SDA5) showed increased drug release was found to be 97.80±1.58% at the end of 60mins in 900 ml of P^H 7.2 Phosphate buffer and 0.5%SLS at 37±0.5 °C. In case of Lumefantrine the optimized formulation SDRF5 released 96.67± 1.26% in 900ml of P^H 1.2, 0.1 N HCl and 0.5%Tween 80.

Conclusion: 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.

Keywords: Solvent evaporation, Solubility, Artemether and Lumefantrine.

INTRODUCTION

Malaria has been described since ancient times as a seasonal periodic fever. The name malaria is originated from Latin's *mal aira* 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]. Mainly majority (~90%) of the people who are living 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 compare 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 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- precipitation), 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 is 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 solubility of poorly water 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 are 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 sulfate, 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 drug for the children, and to the persons who are resistant towards the anti malarial drug chloroquine. The treatment by using these drugs is a Radial treatment (Treatment given for 3days). 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, PEG 6000, 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 30mins 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 1: It shows Formulation table of solid dispersion of Artemether

Formulation code	Carrier	Drug: Polymer	Drug (mg)	Polymer (mg)	Aerosil (mg)	Acetone (ml)
SDA1	POLOXAMER	1:1	20	20	10	q.s
SDA2	PEG 6000	1:1	20	20	10	q.s
SDA3	PVP K-30	1:1	20	20	10	q.s
SDA4	PVP K-30: PEG 6000	1:2:3	20	40:60	10	q.s
SDA5	PVP K-30: PEG 6000	1:3:2	20	60:40	10	q.s

Table 2: It shows Formulation table of solid dispersion of Lumefantrine

Formulation code	Carrier	Drug: Polymer	Drug (mg)	Polymer (mg)	Aerosil (mg)	Chloroform (ml)
SDR1	POLOXAMER	1:1	120	120	10	q.s
SDR2	PEG 6000	1:1	120	120	10	q.s
SDR3	PVP K-30	1:1	120	120	10	q.s
SDR4	PVP K-30: PEG 6000	1:2:3	120	240:360	10	q.s
SDR5	PVP K-30: PEG 6000	1:3:2	120	360:240	10	q.s

Evaluation parameters

FT-IR studies [14]

FTIR 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°-65.003°, 2θ 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^H 7.0), P^H 1.2, 0.1N HCl and phosphate buffer at P^H 7.2 separately. The contents of the test tubes were sonicated for 20 min at room temperature in an ultra sonic 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 Watt's man filter paper. The filtrate was analyzed using spectrophotometrically (UV-1800 Shimadzu) at a λ_{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^H 7.0) was used as solvent for both Artemether and Lumefantrine.

The filtrate was analyzed using spectrophotometrically (UV-1800 Shimadzu) at a λ_{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, Electrolab, Mumbai, India) in 900ml of P^H 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^H 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 λ_{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.

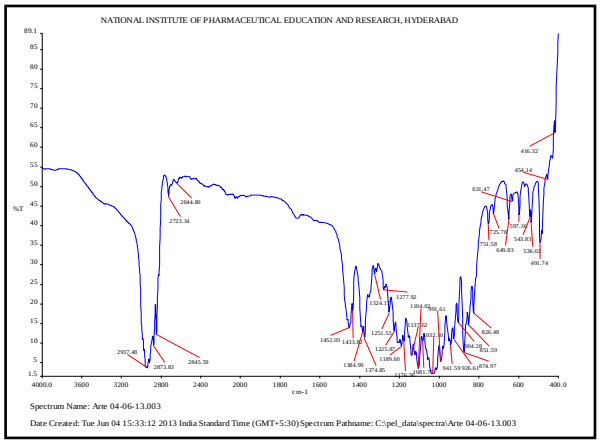

Fig. 1: it shows ftir spectra of pure drug of artemether

The FTIR results from optimized formulation SDAF5 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, **1343.33cm^{-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.

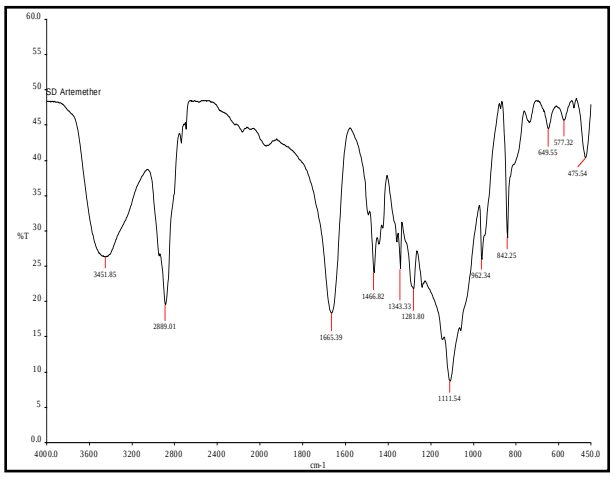

Fig. 2: it shows ftir spectra of solid dispersed artemether In case of Lumefantrine

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.

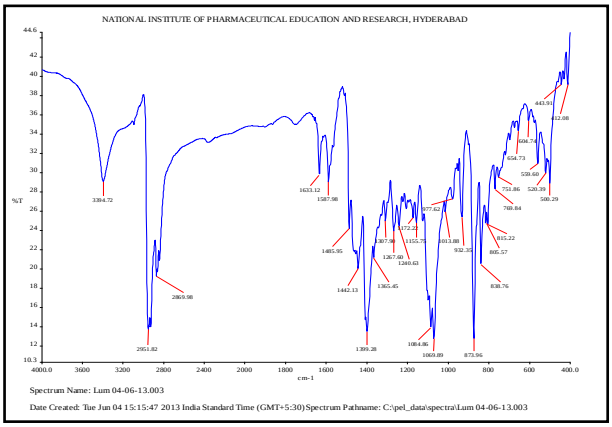

Fig. 3: it shows ftir spectra of pure drug of lumefantrine

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.

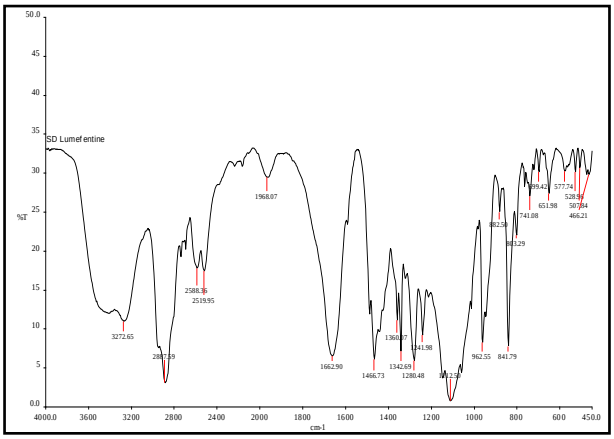

Fig. 4: it shows ftir spectra of solid dispersed lumefantrine

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 Valizaden *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°, 4.66°, 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.

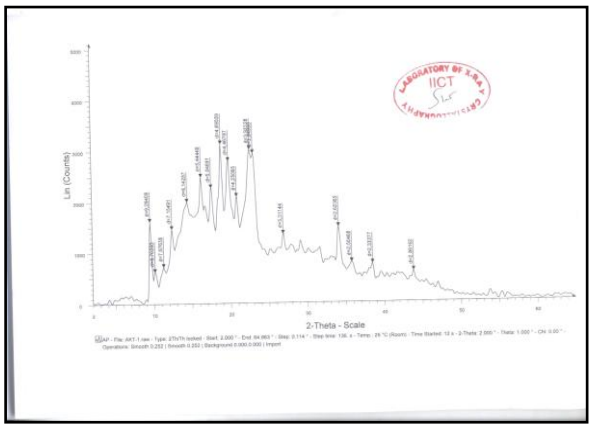

Fig. 5: it shows pxrd studies of artemether

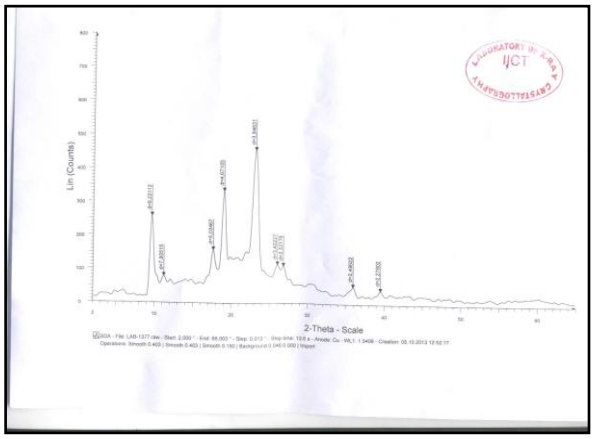

Fig. 6: it shows pxrd studies of solid dispersed artemether

Preliminary Solubility studies of Artemether and Lumefantrine

Solubility studies of Artemether and Lumefantrine was carried out in P^H 1.2 using 0.1N HCl distilled water (P^H 7.0) and phosphate buffer solution P^H 7.2. The solubility of Artemether was found to be 1.67ug/ml, 1.18ug/ml and 3.47ug/ml in P^H 1.2, 7.0, 7.2 respectively. The solubility of Lumefantrine was found to be 2.46ug/ml, 0.44ug/ml and 0.68ug/ml in Acidic P^H 1.2, Neutral P^H 7.0 and Phosphate buffer solution P^H 7.2.

Solubility Study

Solubility of Artemether increased by 33.22 times in case of PVP K-30(39.20ug/ml) compared to POLOXAMER (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 incase in solubility of Artemether and the solubility increased by 50.72times (59.85ug/ml) in case of solid dispersion SDA5 which contains 3:2 ratio of PVP K-30 and PEG 6000 were shown in Figure. 9

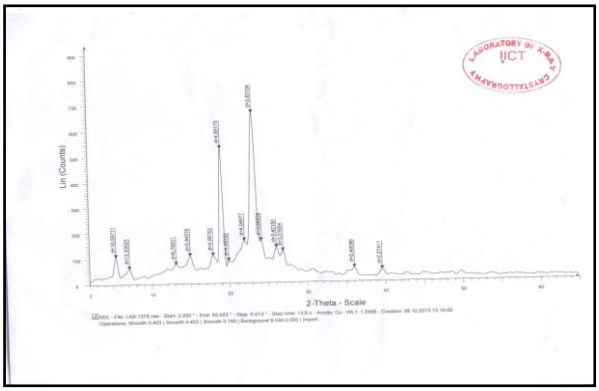

Fig. 7: it shows pxrd studies of pure lumefantrine

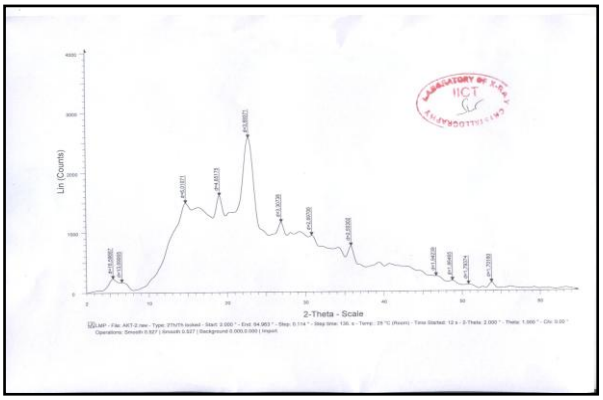

Fig. 8: it shows pxrd studies of solid dis persed lumefantrine.

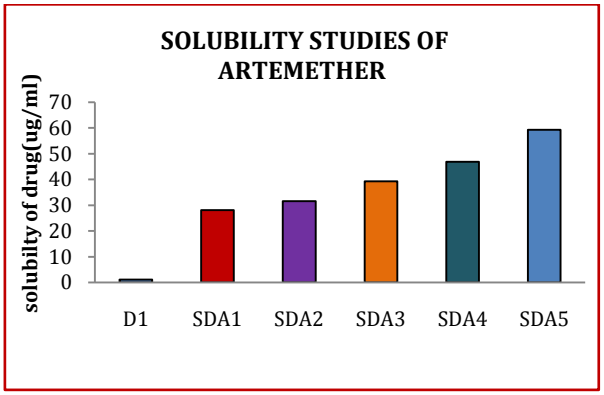

Fig. 9: it shows solubility study of artemether in distilled water (ph 7.0)

In case of Lumefantrine solubility increased by 33.45 times in case of PVP K-30(11.76ug/ml) compared to POLOXAMER (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 incase in solubility of Artemether and the solubility increased by 67.38times (29.65ug/ml) in case of solid dispersion SDA5 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 P^H 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 compare 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 of formulation SDA5 is more compare 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.

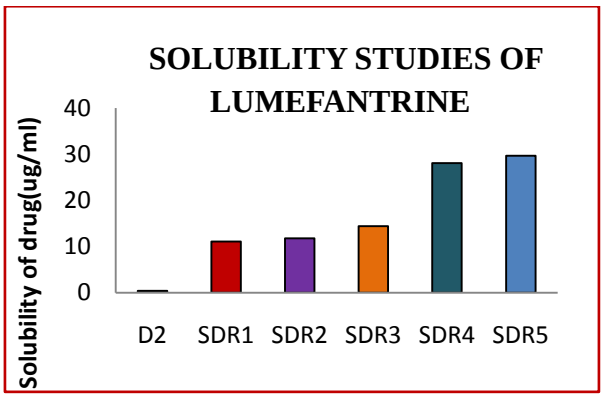

Fig. 10: it shows solubility study of lumefantrine in distilled water (ph 7.0)

In case of Lumefantrine, *In vitro* dissolution studies of solid dispersions and pure Lumefantrine was carried in PH 1.2, 0.1N HCl and 0.5%Tween 80. The percentage of drug release from the formulation containing single polymer SDR1-SDR3 at the end of 60th minute was 43.12%, 51.33% and 66.96 % only. In case of Optimized formulation SDR5, containing PVP K-30 and PEG 6000 in the ratio of 3:2 released 96.67% drug at the end of 60th minute. This increased percentage of drug released of formulation SDR5 is more and time taken to release is less compare to pure Lumefantrine I.e.16.95%drug released at the end of 120 minutes. The dissolution profiles of all the formulations and pure Lumefantrine are shown in figure.12. Though the dissolution study for solid dispersions is 60th minute still the dissolution is carried out for 120minutes, The reason behind for carrying out dissolution studies of Lumefantrine up to 120 minutes because Lumefantrine takes 120mins to reach for its maximum absorption, after which it showed drastic drop it is because of precipitation of Lumefantrine due to super saturation this was proven by Sagar Narayankar**. But in case of solid dispersion formulation the time taken to reach to its maximum absorption is only 60minutes.To study the increased dissolution rate of the solid dispersed drug with that of pure drug the dissolution is carried until 120minutes.

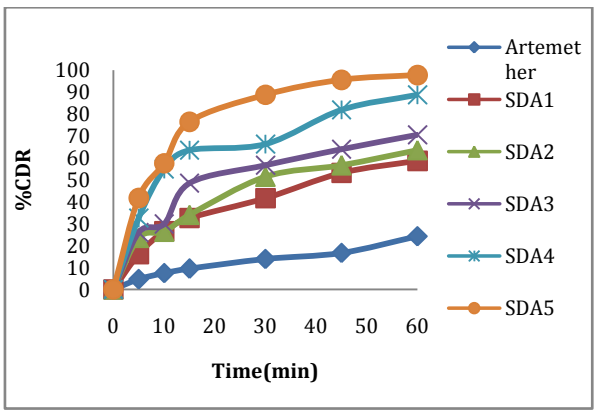

Fig. 11: it shows *in vitro* release profile of artemether in ph 7.2 phosphate buffer and 0.5% sls from solid dispersion formulations and pure artemether.

This increased dissolution rate of formulations of Artemether and Lumefantrine may be due 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.

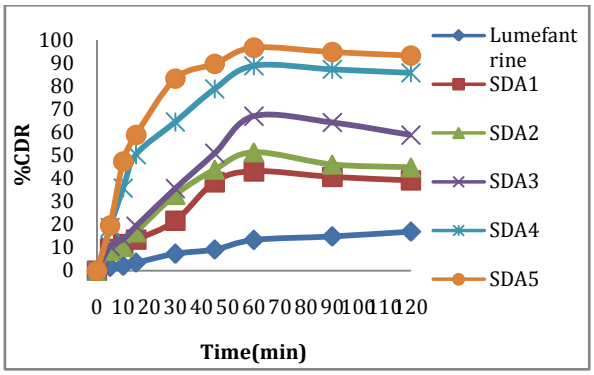

Fig. 12: it shows *in vitro* release profile *of* lumefantrine in ph 1.2, 0.1n hcl and 0.5% tween 80 from solid dispersion formulations and pure lumefantrine.

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, POLOXAMER. 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.

ACKNOWLEDGEMENTS

The author wishes Mylan, Hyderabad, Andhra Pradesh, India for gift sample of Artemether and Lumefantrine drugs and the Management of Trinity College of Pharmaceutical Sciences, Peddapally, Karimnagar Dist, Andhra Pradesh, India, for providing all the support and encouragement to carry out this study.

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