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Original Article

FORMULATION AND EVALUATION OF LUMEFANTRINE CAPSULE PREPARED BY USING LIQUISOLID TECHNIQUE

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ABSTRACT

Objective: The objective of present research work was to formulate and evaluate of Lumefantrine capsule by using novel liquisolid technique to give increased dissolution rate of poorly water-soluble drug Lumefantrine.

Methods: Formulation of lumefantrine capsule using drug solution and suspension method was used. Different liquisolid formulations were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compressible admixture. Liquisolid capsule formulation F-1 to F-9 were prepared by using different type and different concentration of non-volatile solvent like PEG-400, Tween 80, propylene glycol and avicels, aerosil as carrier and coating material respectively.

Results: The liquisolid formulation were within the acceptable limits and drug release rates of all prepared liquisolid were distinctly higher as compared to pure drug. Lumefantrine shows maximum solubility in tween 80 as a non-volatile solvent. All the preformulation parameters were evaluated such as organoleptic characterization of the drug sample, melting point, pH, identification of drug samples by using UV spectroscopy and FTIR analytical method, preparation of calibration curves, solubility studies of drug sample like qualitative, quantitative and pH-dependent solubility of the drug in a buffer solution of different pH. They were further processed for solid-state characterization such as, DSC and SEM and the results confirmed the transformation of native crystalline nature of drug to an amorphous state. FTIR analysis also confirmed no drug-excipient interaction. Liquisolid formulations showed improved *in vitro* dissolution behaviour of lumefantrine over that of pure drug.

Conclusion: From this study, it was concluded that liquisolid method is a promising alternative for improvement of dissolution property of water-insoluble drugs.

Keywords: Lumefantrine, Avicel, Proplylene glycol, Polyethylene glycol-400, Tween 80, Aerosil

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INTRODUCTION

The objective of present research work is to enhance the aqueous solubility of poorly water-soluble drug lumefantrine using the liquisolid technique. Initially, liquid medication has to be prepared where the drug is dispersed in a nonvolatile solvent. These liquid medication is further combined with calculated quantities of selected carrier and coating materials to form free-flowing, dry-looking, non-adherent and readily compressible powders [1]. This can be further formulated either as immediate-release tablets (liquid solid compacts) or encapsulated in hard gelatin capsules.

Lumefantrine also known as Benflumetol, is an antimalarial drug. Lumefantrine is a long-acting antimalarial drug and is highly effective in the treatment of resistant *P. falciparum malaria.* It belongs to BCS Class IV having low solubility and low permeation. Hence it is necessary to increase the solubility of the drug in order to increase bioavailability to show effective pharmacological action. The drug is having low solubility of about 0.092 mg/ml and oral bioavailability is around 18%. Lumefantrine has been included in Indian pharmacopeia of essential drug for the treatment of malaria but major drawback of the drug is low water solubility [2]. Lumefantrine is an erythrocytic schizontocide and acts by inhibiting haeme polymerization in the food vacuole of plasmodia and hence used as antimalarial drug. The oral formulation of this drug was incompletely absorbed and its bioavailability is also low. So in the treatment of malarial infection there is always need of repeated administration of this drug by oral route. Often it is orally administered and used in combination with artemether in the form of fixed dosed tablets for improved efficacy in treating malaria [3]. Different solubility enhancement techniques have been developed till present but nowadays researchers are mainly focusing on novel solubility enhancement techniques to improve solubility of drug. Bioavailability of oral preparation is highly depending on the solubility [4]. Liquisolid drug delivery system is a novel and most important method to increase the solubility of water-insoluble solid drug [BCS Class II and IV]. It can enhance dissolution rate as well as bioavailability of drug. Rapid release rates can be obtained in liquisolid formulations and these can be efficiently used for water-insoluble/poorly soluble drugs [5]. The liquid medication (solid drugs in nonvolatile solvent) contains drug in the form of solubilized or in molecularly dispersed state [6]. It can be further converted to free-flowing, non adherent and readily compressible powders with use of carrier and coating materials. Owing to increased wetting property and increased surface area for dissolution, liquisolid systems of water-insoluble drugs show improved dissolution profile [7].

MATERIALS AND METHODS

Material

Lumefantrine was kindly gifted by Cipla pharmaceuticals (Pithampur). Aerosil 200 and Avicel PH102 were gift samples from AVL pharmaceuticals (Hyderabad, India) and Signet Chemicals Corporation (Mumbai, India). Tween 80, propylene glycol (PG), polyethylene glycol (PEG400) were purchased from SD Fine-Chem Ltd (Mumbai, India).

Methods

Preformulation studies

Pre-formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Spectrophotometric analysis

Preparation of calibration curve of lumefantrine in methanolic HCl (λmax 332 nm)

A standard stock solution of Lumefantrine was prepared by dissolving 100 mg of drug in 100 ml of 0.1M methanolic HCl (1000µg/ml). From

the above stock solution, 10 ml was taken and diluted upto 100 ml in methanolic HCl (100µg/ml). From the above solution 1, 2, 3, 4, 5 and 6 ml was taken and diluted up to 10 ml with methanolic HCl to get series of solutions in a concentration range from 10 to 60 µg/ml of Lumefantrine. Absorbance was noted using UV-VIS Spectrophotometer at λmax of 332 nm against a blank (methanolic HCl) [8, 9].

Drug-excipient compatibility studies

While developing a new formulation, it is necessary to check the drug compatibility with the carrier or excipients used and that the drug has not undergone any degradation when it passes through the various processes. Suitable evidential experiments are conducted to justify and prove the intactness of drug in the formulations [10]. A small amount of drug substance with excipients were physically mixed in 1:1, 1:2, 1:3 ratio and placed in a vials which were then properly capped and sealed [62]. The vials of each sample were kept at room temperature (25 °C) and 40 °C for one month period. After storage, the sample was observed physically for liquiefaction, caking, colour, odour, discolouration.

Saturation solubility studies

To select the best non-volatile solvent to dissolve lumefantrine, solubility studies of lumefantrine were carried out in three different non-volatile solvents, i.e., PEG400, tween 80, and propylene glycol. Saturated solutions were prepared by adding an excess drug to the vehicles and shaking on the incubator shaker for 48 h at 25+1 °c under constant vibration [11]. After shaking, the solutions were filtered through whatman filter paper, diluted with 0.1 M methanolic HCL water and analyzed by UV-spectrophotometer (U-V1800 Shimadzu Corp., Japan) at a wavelength of 332 nm against blank (blank sample contained the same concentration of specific solvent without drug). Six determinations were carried out for each sample and the mean values along with standard deviations were reported.

Application of the mathematical model for preparation of liquisolid systems

It is defined as the ratio of liquid medication (w) to the weight of coating material (q). It is determined by dissolving or dispersing the drug in non volatile solvent and to this carrier coating material admixture is added and blended. The amount of carrier-coating admixture is used to convert free flow powder and is determined by using the following formula.

$$L_f = W/Q$$

Where, W = Weight of liquid medication, Q = Weight of carrier material, the Φ value is for calculating excipients quantities. Equation is,

$$L_f = \Phi+\Phi\ (1/R)$$

Where Φ and Φ are values of carrier and coating material [12]. It is used to calculate the amount of carrier and coating material in each formulation. The excipients ratio R of powders is defined as the ratio of carrier and coating material present in the formulation. R is suitably selected for successful formulation.

Where,

$$R= Q/q$$

Q = weight of carrier, q = coating material [13, 14].

Calculation of load factor

In a liquisolid system, the amount of liquid retained by the carrier and coating materials depends on the excipients ratio (R) while maintaining acceptable flow and compression properties. The excipient ratio R (R=Q/q) of powder is defined as a ration between the weights of the carrier (Q) and coating (q) present in the formulation [15]. Preparation of a liquisolid system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier material is not exceeded. This characteristic amount of liquid is termed as liquid load factor (L_f)[16]. The liquid load factor (L_f) is defined as the weight ratio of liquid medication (W) and carrier powder (Q) in the system (i.e., L_f =W/Q). To calculate the loading factor,non-volatile solvent (liquid medication without drug) was added to 10 g carrier material and blended for 1 min. The above procedure was repeated until a powder with acceptable flow rate was obtained.

Binding capacity of adsorbents for the solvents

Binding capacity is defined as the capacity of powder excipients to hold liquid without a change in their flow properties. It was determined by the following simple methods. A constant weight of 5 g of different powder excipient (Avicel PH102) were put into a mortar and non-volatile was added in increments of 0.01 ml. The mixture was triturated after each addition to help distribution of the liquid throughout the powder particles. Addition of liquid was continued until lumps appeared in the powder mixture [17].

Formulation of lumefantrine capsule using drug solution and suspension method

Various types of non-volatile solvents are chosen for dissolving the drug. Various ratios of carrier to coating materials are selected. Desired quantities of drug and non-volatile solvents were accurately weighed in a beaker and then stirred continuously until a homogenous drug solution/suspension was obtained [18]. Selected amounts of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar. The mixing procedure was conducted in three stages during the first stage, the system was subjected to sonication for approximately one minute in order to evenly distribute the drug with the nonvolatile liquid. In the second stage, calculated quantities of carrier material were added to the liquid medicament and evenly spread as a uniform layer on the surfaces of the mortar [19]. Approximately 5 min to allow the drug solution to be absorbed in the interior of the powder particles. In the third stage, the coating material was added and triturated. Fill the formulation in hard gelatin capsule producing the final liquisolid formulation [20].

Flow properties of liquisolid powders

Angle of repose (θ)

The angle of repose was determined using fixed funnel method. Funnel is fitted vertically with stand of height. The opening end of funnel is closed with the thumb until drug was poured. The 5 gm of sample was poured into funnel that can be rained vertically until a maximum concentration height (h) was obtained. radius of the heap (r) was measured and the angle of repose (ɵ) was calculated using the formula[21]:

$$\text{Tan } ɵ = (h/r)$$

The range indicates that if<20 ° it is excellent. If the range between 20-30 ° then good and its range 30-40 ° it is fair to passable.

Carr's index

The simplest way for measurement of free flow of powder is compressibility indication of the ease with which a material can be induced to flow is given by compressibility index. it is a simple test to evaluate the bulk density and tapped density of powder and the rate at which it packed down. The value below 15% indicates a powder which gives rise to good flow properties where's about 25% indicate poor flowability, which calculated using formula.

$$\text{Compressibility index} = \text{Tapped Density–Bulk Density/Tapped Density} \times 100$$

Hausner ratio

Hausner ratio is an index of ease of powder flow. Hausner ratio is the ratio of true density to bulk density. Lower the value of hausner ratio, better is the flow property. Poeder with hausner ratio less than 1.18, 1.19, 1.25, 1.3-1.5 and greater than 1.5 indicate excellent, good, passable, and very poor respectively. It is calculated by following formulae.

$$\text{Hausner Ratio} = \text{Tapped density/Bulk density}$$

Bulk density

Weight accurately 10g of the powder sample, which was previously passed through #40 sieve and transferred in 50 ml of the graduated cylinder. Careful passed the level the powder without compacting,

and read the unsettled apparent volume (V_o). Calculate the apparent bulk density in gm/ml by the following formula [22].

Bulk density = Weight of powder/bulk volume

Tapped density

Weight accurately 10g of powder sample which was previously passed through #20 sieve and transfer in 50 ml graduated cylinder containing known mass (10 gm) of the sample was tapped for 100 times using mechanically tapped density tester [23].

Tapped density = Weight of powder/Tapped volume

FTIR study

The IR analysis of the sample was carried out for qualitative compound identification. In ATR (Attenuated Total Reflectance), the solid material is placed onto the small crystal area. In this instrument IRAffinity-1, (Shimadzu, Japan) diamond being the preferred choice for most applications because of its robustness and durability [24]. After solid has been placed on the crystal area, the pressure arm is positioned over the crystal/sample area. Force is applied to the sample, pushing it onto the diamond surface. Transmittance was measured from wave number 4000 cm^{-1} to 400 $^{-1}$using Happ-Gensel apodization.

Differential scanning calorimetry (DSC)

Thermograms were recorded using a differential scanning calorimeter (Perkin-Elmer India Pvt. Ltd.). Samples (5-10 mg) were weighed and hermetically sealed in flat-bottomed aluminium pans. These samples were heated over a temperature range of 50-400 °C in an atmosphere of nitrogen (200 ml/min) at a constant rate of 10 °C per minute, with alumina being the reference standard.

Scanning electron microscopy (SEM)

Scanning Electron Microscopy (SEM) are very useful in determining shape and morphology of lipid nanoparticles and allow determination of particle size and distribution. SEM uses electrons transmitted from the specimen surface. The formulation was poured into the circular aluminium plate and dried in vacuum oven to form a dry film which was then observed under the scanning electron microscope (FEI, Quantum 200E Instrument)[26].

Determination of drug content

Drug content was determined by dissolving 60 mg of liquisolid formulation in methanolic HCL into 50 ml of measuring cylinder, and suitability diluted with pH 1.2 (0.1N HCl) buffer, and then sonicated for 15 min followed by filtered through the whatman filter paper and analyzed by UV spectrophotometer at 332 nm against pH 1.2 (0.1N HCl) buffer as a blank. Readings were taken in triplicate and observation are recorded [27].

***In vitro* dissolution studies**

In vitro dissolution studies of liquisolid powder was carried out using a USP dissolution apparatus II Rotating Paddle type (Electrolab-DBK, Mumbai, India) at speed of 50 rpm using 900 ml of pH 1.2, 0.1N HCL at 37 °C as dissolution medium[28]. One capsule was used in each test. Accurately weighed the amount of liquisolid capsule were immersed in a dissolution medium consisting of in 900 ml of pH 1.2, 0.1N HCL dissolution medium at 37 °C. An aliquots of the dissolution medium 5 ml was withdrawn at specific time intervals (5, 10, 15, 30, 45 and 60 min) and replacing the same amount with the fresh medium in order to keep the total volume constant. Filtered over a whatman filter paper. The samples were analyzed using spectrophotometrically (UV-1800 Shimadzu) at a λmax of 332 nm.

Stability study

The selected liquisolid formulations of lumefantrine were subjected to accelerated stability study as per ICH guideline. The formulations were filled in 10 ml glass vials were plugged and sealed. The vials were kept at different temperature conditions such as room temperature (25 °C) and 40+2 °C/75+% RH using desiccator containing calcium chloride, for a period of 1 mo [29]. At definite time intervals, the samples were visually examined for any physicals change. The drug content and dissolution rate was estimated after one month [30].

RESULTS AND DISCUSSION

Estimation of lumefantrine

The calibration curve was obeyed Beer Lambert's law in the concentration range of 0-50 µg/ml (R2 = 0.999).

Table 1: Preformulation studies of lumefantrine

Parameters	Results
Organoleptic Properties	yellow crystalline powder, Odourless, Bitter in taste
Melting Point	130 °C
pH	8.1
Partition Coefficient	2.9

Drug-excipient compatibility studies

Table 2: Drug excipient compatibility studies

Drug excipients ratio	Observation at different storage conditions								Remarks
	25 °C				40 °C				
	Duration (weeks)								
	1	2	3	4	1	2	3	4	
Drug: Avicel (1:1)	N	N	N	N	N	N	N	N	Accepted
Drug: Avicel (1:2)	N	N	N	N	N	N	N	N	Accepted
Drug: Avicel (1:3)	N	N	N	N	N	N	N	N	Accepted
Drug: Aerosil (1:1)	N	N	N	N	N	N	N	N	Accepted
Drug: Aerosil (1:2)	N	N	N	N	N	N	N	N	Accepted
Drug: Aerosil (1:3)	N	N	N	N	N	N	N	N	Accepted

N=No change in color or physical appearance

Saturated solubility studies of non-volatile solvents

Saturation Solubility Studies were carried out to select the best solvent for the liquisolid system. Following table gives the results of solubility studies. Lumefantrine showed maximum solubility in Tween 80, hence the same was selected as non–volatile solvent.

The table shows the results of solubility studies.

Table 3: Solubility of lumefantrine in various solvents

S. No.	Solvents	Solubility % (mg/ml)
1	Distilled water	0.092
2	Propylene glycol	0.347
3	PEG-400	0.389
4	Tween 80	0.548

Application of the mathematical model for preparation of liquisolid systems

Table 4: Composition of optimized lumefantrine liquisolid capsule formulation according to the mathematical model

Batch code	Drug (mg)	W (mg) Non-volatile solvent		R R=Q/q	L_f L_f =W/Q	Avicel ®PH 101 (mg) Q=W/l_f	Aerosil (mg) q=Q/R	Total weight (mg)
F1	60	100		1.66	1	100	60.24	322.9
F2	60	110	PEG-400	2	0.91	131	60	363.91
F3	60	120		2.5	0.8	187.5	60	430.8
F4	60	100		1.66	1	100	60.24	322.9
F5	60	110	PG	2	0.91	131	60	363.91
F6	60	120		2.5	0.8	187.5	60	430.8
F7	60	100		1.66	1	100	60.24	322.9
F8	60	110	Tween 80	2	0.91	131	60	363.91
F9	60	120		2.5	0.8	187.5	60	430.8

W … weight of liquid medication; Lf … liquid load factor; Q … weight of carrier material; q … weight of coating material Q=W/l_f. q=Q/R; R … carrier: coat ratio (R=Q/q), Lf=W/Q.

Determination of equilibrium solubility of liquisolid formulations

The solubility of Lumefantrine was found to be enhanced in the Liquisolid formulation. The formulation prepared with polyethene glycol 600, propylene glycol and tween 80, as non-volatile solvents and Avicel and aerosil used as a carrier and coating materials. Results indicated that the solubility enhancement was best in formulation F9 which is in the ratio of 21.41%.

Table 5: Saturation solubility study of various formulations

S. No.	Formulation code	Saturation solubility (µg/ml) at 37+1 °C in water	Percentage solubility enhancement (%)
1	Pure Lumefantrine	0.092	-
2	F-1	0.162	17.60
3	F-2	0.152	16.52
4	F-3	0.158	17.17
5	F-4	0.162	17.60
6	F-5	0.179	19.45
7	F-6	0.181	19.67
8	F-7	0.189	20.54
9	F-8	0.192	20.86
10	F-9	0.197	21.41

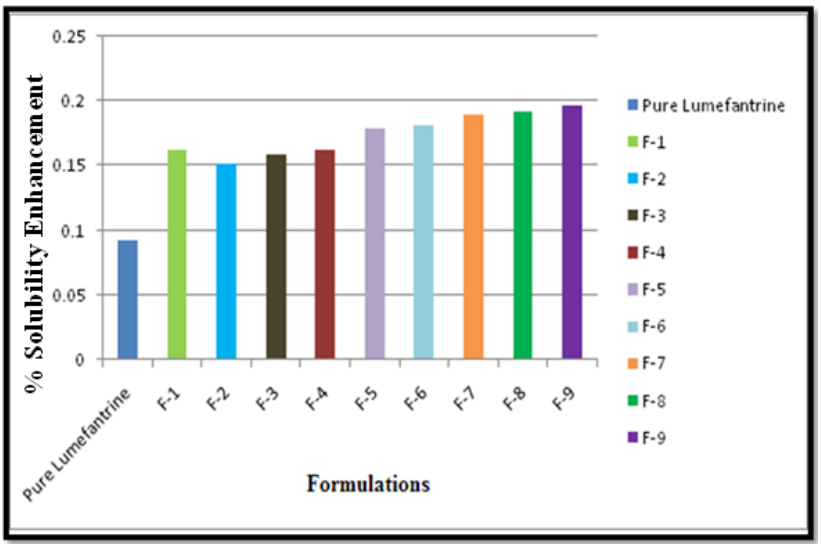

Fig. 1: Comparison of solubility of pure drug with formulation F1 to F9

Flow properties of liquisolid powders

Table 6: Determination of flow properties of the liquisolid powder

Batch No	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner's ratio	Carr's index (%)	Angle of repose (ɵ)
F1	0.396	0.448	1.14	12.15	26 °.22
F2	0.395	0.429	1.12	12.88	26 °.92
F3	0.392	0.449	1.17	12.71	27 °.22
F4	0.383	0.444	1.18	14.61	27 °.82
F5	0.379	0.448	1.18	15.46	28 °.31
F6	0.378	0.450	1.16	15.41	28 °.24
F7	0.377	0.446	1.13	12.14	29 °.79
F8	0.379	0.440	1.12	12.35	30 °.44
F9	0.395	0.450	1.13	11.01	31 °.41

FT-IR spectra of pure drug

The appearance or disappearance of peaks and/or the shift of their positions are often indications of interactions such as hydrogen bonding. Lumefantrine presented characteristic peak at 3393.64 cm^{-1} due to NH, did not deviate from its position in presence of excipients can be concluded as no interaction between drug and excipients.

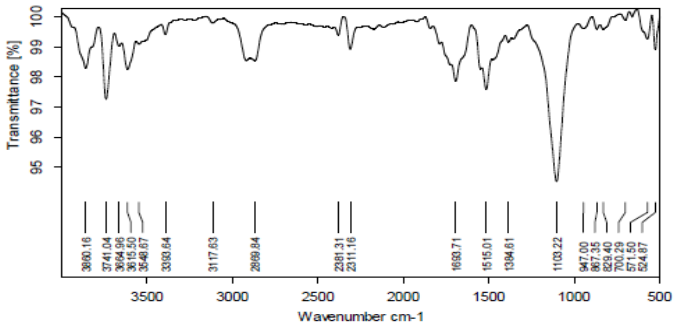

Fig. 2: FT-IR spectra of pure drug

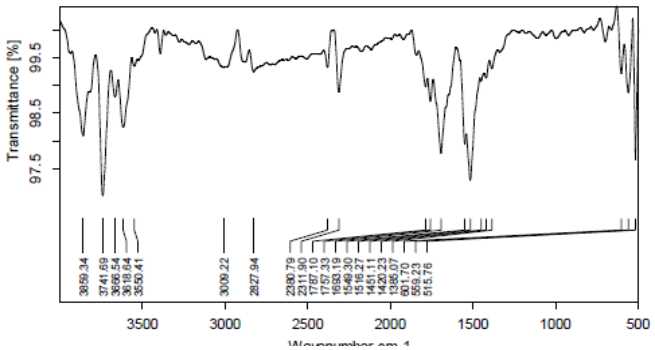

Fig. 3: FT-IR Spectra of MCC

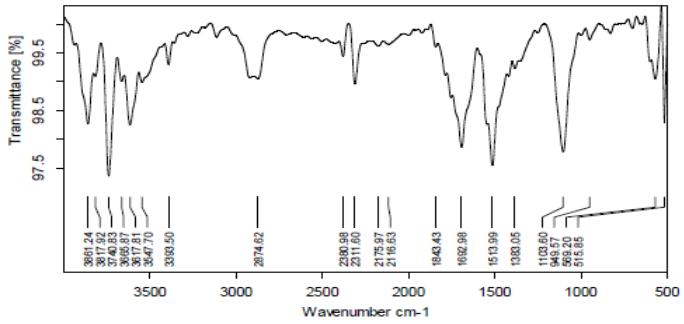

Fig. 4: FT-IR spectra of formulation F-9

DSC study

DSC thermogram of Lumefantrine exhibited melting point at 128-132 °C. The mixture of drug, and an excipient, and Physical mixture (without drug) which was kept in an accelerated condition of 40 °C/75% RH for 30 d and subjected to DSC analysis. The characteristic melting point of Lumefantrine does not deviate from 128-132 °C that predicts that there is no interaction between drug and excipients.

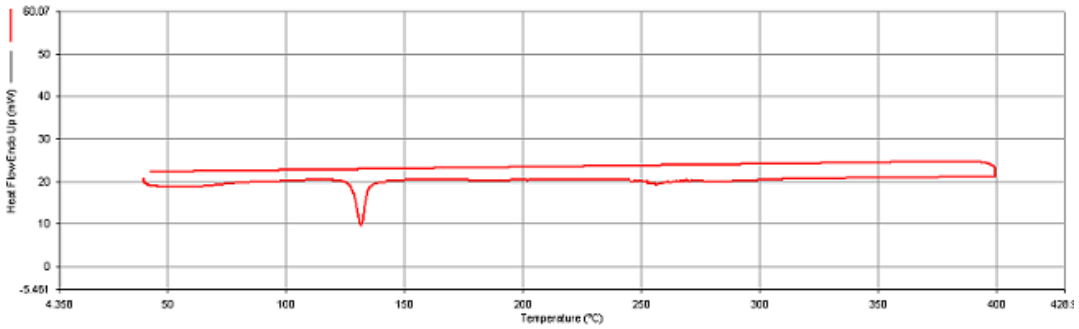

Fig. 5: DSC of pure drug lumefantrine

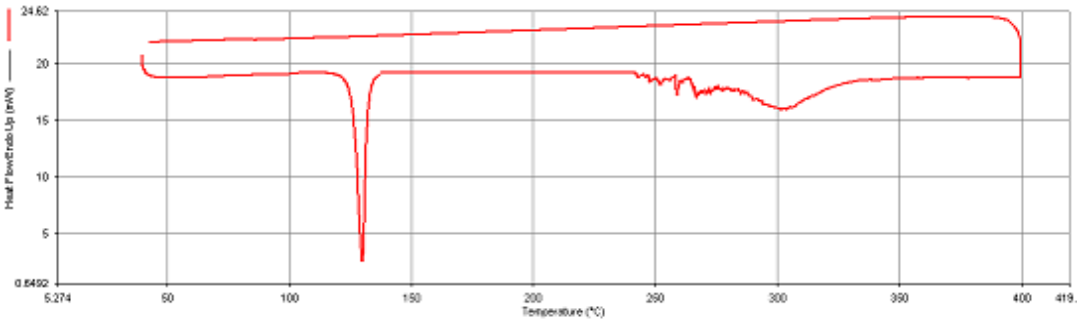

Fig. 6: DSC of liquisolid formulation F9

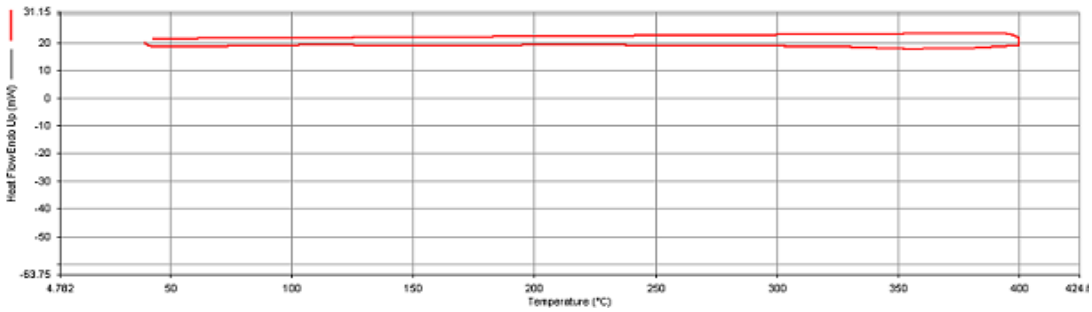

Fig. 7: DSC of microcrystalline cellulose (Avicel)

SEM analyses

SEM analysis of lumefantrine, formulation F9 was performed to determine the surface morphology of drug in the liquisolid system. The disappearance of crystalline nature of drug indicates that the drug is solubilised in the system. Lumefantrine showed large crystalline blocks, where liquisolid formulation was found to be without sharp edges.

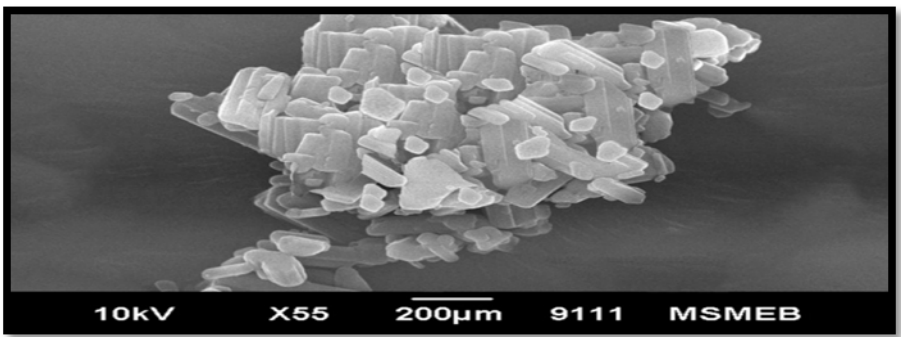

Fig. 8: SEM image of drug

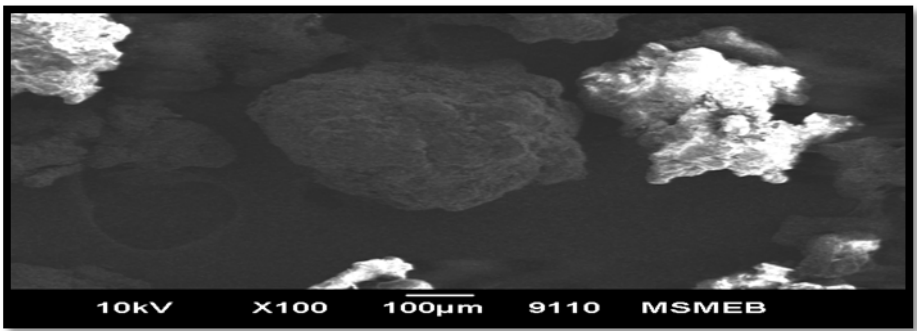

Fig. 9: SEM image of liquisolid formulation F-9

Determination of drug content

The drug content estimation was done to ensure uniform distribution of the drug. The drug content of liquisolid powder of Lumefantrine was performed for all the prepared formulated in the table. Obtained results indicate that that in the all the formulations drug content was uniform a ranged between 90.00% to 98.95% which was analyzed spectrophotometrically at λmax 332 nm.

***In vitro* dissolution rate studies**

The dissolution rate of Lumefantrine from its Liquisolid capsule significantly higher than the pure drug.

Table 7: Drug content of the various formulation

S. No.	Formulation code	% Drug content
1	F-1	86.00
2	F-2	88.11
3	F-3	90.62
4	F-4	92.90
5	F-5	93.05
6	F-6	94.20
7	F-7	95.76
8	F-8	97.07
9	F-9	98.54

Table 8: *In vitro* release of lumefantrine liquisolid capsule formulation F1-F9

Time	Drug	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
5	4.5	15	15	17.25	19.5	23.25	25.5	26.25	30	30.75
10	10.5	35.25	41.25	39	42	46.5	46.5	45.75	47.25	48.75
15	12.75	61.5	63	66.75	70.5	74.25	78	78	79.5	80.25
30	23.25	76.5	78	78.75	81.75	83.25	86.25	89.25	90.75	92.25
45	32.25	81.75	84	84.75	85.5	87	90.75	94.5	95.25	96
60	45.75	87	89.25	90.75	93	93.75	94.5	95.25	96	97.5

Stability studies

Results of stability studies showed that there was no significant change in organoleptic properties, drug content, *In vitro* study of Lumefantrine liquisolid formulation. Thus the result showed that the formulations have good stability.

CONCLUSION

It can be concluded that with the carefully designed experimental technique enhance the solubility of the poorly water-soluble drug can be improved by using the novel liquisolid technique. This technique is a promising alternative for the formulation of BCS class-II and class-IV drugs, which are poorly soluble. The method is simple and effective and can be used on an industrial scale. The production of the Liquisolid system does not involve the application of any specialized types of equipment, hence it is an economical, yet very effective tool for enhancement of dissolution rate of poorly soluble drugs. It is a successful and simple method to prepare Liquisolid capsule to enhance its aqueous solubility and dissolution rate. Nature and amount of carrier and coating materials used to played important role in the enhancement of dissolution rate. The use of a non-volatile solvent in the formulation of Liquisolid capsule causes increased wettability of water-insoluble drug Lumefantrine and ensures molecular dispersion of the drug in the formulation. Dissolution studies data reveals due to the presence of liquisolid formulation drug the increased dissolution profile and enhance solubility compare to the pure drug.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest

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