FORMULATION AND EVALUATION OF LUMEFANTRINE CAPSULE PREPARED BY USING LIQUISOLID TECHNIQUE

AMREEN KHAN*, SHIKHA AGRAWAL

Department of Pharmaceutics, Swami Vivekanand College of Pharmacy, Indore 452020, Madhya Pradesh, India

Email: amreenk82@gmail.com

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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 medications are 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 pharmacopoeia of essential drug for the treatment of malaria but major drawback of the drug is low water solubility [2]. Lumefantrine is an erythrocytic schizonticide 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 dosage 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].

MATERIALS AND METHODS

Material

Lumefantrine was kindly gifted by Cipla pharmaceuticals (Pithampur). Aerosil 200 and Avicel PH102 were gift samples from AVL (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 (Amax 332 nm)

A standard stock solution of Lumefantrine was prepared by dissolving 100 mg of drug in 100 ml of 0.1M methanolic HCl (100µg/ml). From
the above stock solution, 10 ml was taken and diluted up to 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 liquefication, caking, colour, odour, discolouration.

**Saturation solubility studies**

To select the best non-volatile solvent to dissolve lumezantrine, solubility studies of lumezantrine were carried out in three different non-volatile solvents, i.e., PEG400, tween 80, and propylene glycol. Saturation 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. The angle of repose (θ) 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 gms 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 (θ) was calculated using the formula [21]:

\[
\tan \theta = \frac{h}{r}
\]

The range indicates that if<20° then good and its range 30-40 ° then 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 free flow properties where’s about 25% indicate poor flowability, which calculated using formula.

\[
\text{Compressibility index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100
\]

**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. Powder with hausner ratio less than 1.18, 1.19, 1.25, 1.35 and greater than 1.5 indicate excellent, good, passable, and very poor respectively. It is calculated by following formulae.

\[
\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**Bulk density**

Weight accurately 10 g 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 \( V_a \). Calculate the apparent bulk density in gm/ml by the following formula [22].

\[
\text{Bulk density} = \frac{\text{Weight of powder}}{\text{bulk volume}}
\]

**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].

\[
\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}
\]

**FTIR study**

The IR analysis of the sample was carried out for qualitative FTIR study. The IR analysis of the sample was carried out for qualitative and durability [24]. After solid has been placed on 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 were 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 max of 322 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+5% 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 (R\(^2\) = 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 | Remarks |
| Drug: Avicel (1:1)    | N     | N     | N                 | N | N | N | N | N | N | N | Accepted |
| Drug: Avicel (1:2)    | N     | N     | N                 | N | N | N | N | N | N | N | Accepted |
| Drug: Avicel (1:3)    | N     | N     | N                 | N | N | N | N | N | N | N | Accepted |
| Drug: Aerosil (1:1)   | N     | N     | N                 | N | N | N | N | N | N | N | Accepted |
| Drug: Aerosil (1:2)   | N     | N     | N                 | N | N | N | N | N | N | N | Accepted |
| Drug: Aerosil (1:3)   | N     | N     | 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 = Q/q | Lf = W/Q | Avicel ®PH 101 (mg) | Aerosil (mg) | Total weight (mg) |
|------------|-----------|--------|----------------------|---------|----------|---------------------|--------------|-------------------|
| F1         | 60        | 100    |                      | 1.66    | 1        | 100                 | 60           | 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/Q; 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 polyethylene 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) | Haussner’s ratio | Carr’s index (%) | Angle of repose (°) |
|----------|-----------------------|------------------------|------------------|------------------|---------------------|
| 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](image)

![Fig. 3: FT-IR Spectra of MCC](image)

![Fig. 4: FT-IR spectra of formulation F-9](image)
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
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 formulations in the table. Obtained results indicate that in all the formulations drug content was uniform and ranged between 90.00% to 98.95% which was analyzed spectrophotometrically at \( \lambda \text{max} \) 332 nm.

**In vitro dissolution rate studies**

The dissolution rate of Lumefantrine from its Liquisolid capsule was 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| 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, 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 play 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 authors have contributed equally.

**CONFLICT OF INTERESTS**

The authors declare that they have no conflict of interest.

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