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Solubility enhancement study of lumefantrine by formulation of liquisolid compact using mesoporous silica as a novel adsorbent

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ABSTRACT

Lumefantrine, exhibits poor bioavailability due to its very low solubility. A liquisolid compact of lumefantrine was prepared with mesoporous silica as a novel coating material. Lactose anhydrous and syloid 244FP were selected as carrier and coating materials respectively. Varying the carrier to coating ratio from 10 to 35, six formulations were prepared and evaluated for tests for tablets. thermal, surface characteristics, surface morphology, and surface area analysis. The tabletability of the formulation lactose to syloid 244FP ratio at 20:1 was found to be the best among all in terms of compression characteristics, faster disintegration, and enhanced dissolution. Hence it can be concluded that the use of a suitable amount of mesoporous silica in the formulation of liquisolid compact could significantly enhance the dissolution of the drug.

Introduction

Lumefantrine, a fluorene derivative, is widely used in the treatment of insipidus malaria caused by *Plasmodium falciparum*. Lumefantrine, a BCS class II drug an efficacious molecule against falciparum, acts as a blood schizonticide. It has low bioavailability due to its poor solubility. The structural formula of lumefantrine is presented in Fig. 1.

A liquisolid system uses a non-volatile solvent to convert the drugs into drug suspensions or solution, followed by mixing with carriers and coating material to form a dry non-adherent, free-flowing, and compressible powder mixture [1].

Mesoporous silica has attracted considerable attention in liquisolid technology to improve the dissolution of the poorly soluble drug due to its specific surface properties, non-toxic nature, and inert characteristics [2]. It has high porosity and a large internal surface area which enable them to adsorb a high quantity of liquid. Its large pore volume, surface area, and narrow pore size distribution can make it suitable to host the liquid solution of the drug in its molecular sieve[3]. Thus, the network of mesopores leads to enhance the dissolution rate, hence bioavailability [4].

Therefore, this study has its uniqueness to establish the potential effect of mesoporous silica in the enhancement of solubility of lumefantrine in its liquisolid compact.

Experimentation

Estimation of drug solubility in various non-aqueous solvents

Four different non-aqueous solvents tween20, PEG400, PEG600, and propylene glycol were selected to estimate the highest solubility of the drug by mechanical shaking method. The solubility was estimated chromatographically after suitable dilution using a mobile phase consisting of 1:1 acetonitrile and 0.1 %w/v formic acid solvent system at 336.9 nm with a developed process (Linearity range- 5–30 µg/ml, Linearity $y = 161965.25x + 8580.58$ and accuracy 99.96 ± 0.01 % in triplicate.

Preparation of liquisolid compacts

The drug was dissolved in PEG400. The carrier and coating material as per the excipient ratio for fifty tablets as mentioned in Table 1 was blended in a porcelain mortar with the drug dispersion, 10 %w/w microcrystalline cellulose and 1 %w/w magnesium stearate. The powder mixture was evaluated for flow property and compressibility. The drug excipient mixture was subjected to direct compression using multi station rotary punching machine (Rimek Minipress I, Karnavati Engineering Pvt. ltd., Gujarat, India). Fifty tablets were prepared for each coded formulation and subjected to evaluation [5].

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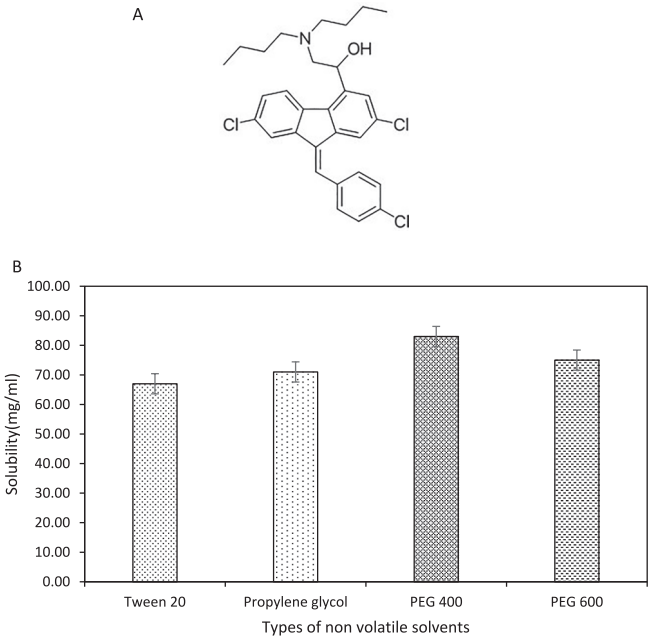

Fig. 1. Structure (A) and Solubility of lumefantrine in different non-aqueous vehicles (B).

Table 1
Composition of liquisolid compact tablet of lumefantrine.

Formulation code	F1	F2	F3	F4	F5	F6
Drug(mg)	120	120	120	120	120	120
PEG 400(ml)	1	1	1	1	1	1
Lactose (mg)	295.45	304.68	309.52	312.5	314.510	315.97
Syloid 244 FP (mg)	29.54	20.31	15.47	12.5	10.48	9.03
Micro Crystalline cellulose (mg)	50	50	50	50	50	50
Mg Stearate (mg)	5	5	5	5	5	5
Excipient ratio (R)	10	15	20	25	30	35
Loading factor (LF)	0.0076	0.0074	0.0073	0.0072	0.0072	0.0072
Total tablet weight (mg)	500	500	500	500	500	500

Evaluation of liquisolid compacts and tablets

Liquisolid compact was evaluated for flow property by determining the angle of repose by fixed funnel method [6]. Compressibility was assessed from the bulk density and true density data.

Evaluation of tablets

The prepared tablets were subjected to various quality control tests like weight variation, content uniformity, hardness, friability, wetting time, disintegration time, and dissolution.

Dissolution testing and determination of dissolution efficiency

In vitro dissolution for the best formulations and pure drug (120 mg) was carried out in 900 ml of hydrochloric acid solution pH1.2 with 1 % Myrj52 in paddle-type apparatus, at 100 rpm and 37 ± 0.5 °C till it reached asymptotes. Sampling was done at 10 min intervals. The samples were analyzed chromatographically in triplicates[7].

Dissolution efficiency was determined by measuring the $AUC_{0\text{-}60min}$ for the best products and the pure drug. Dissolution efficiency (DE) was

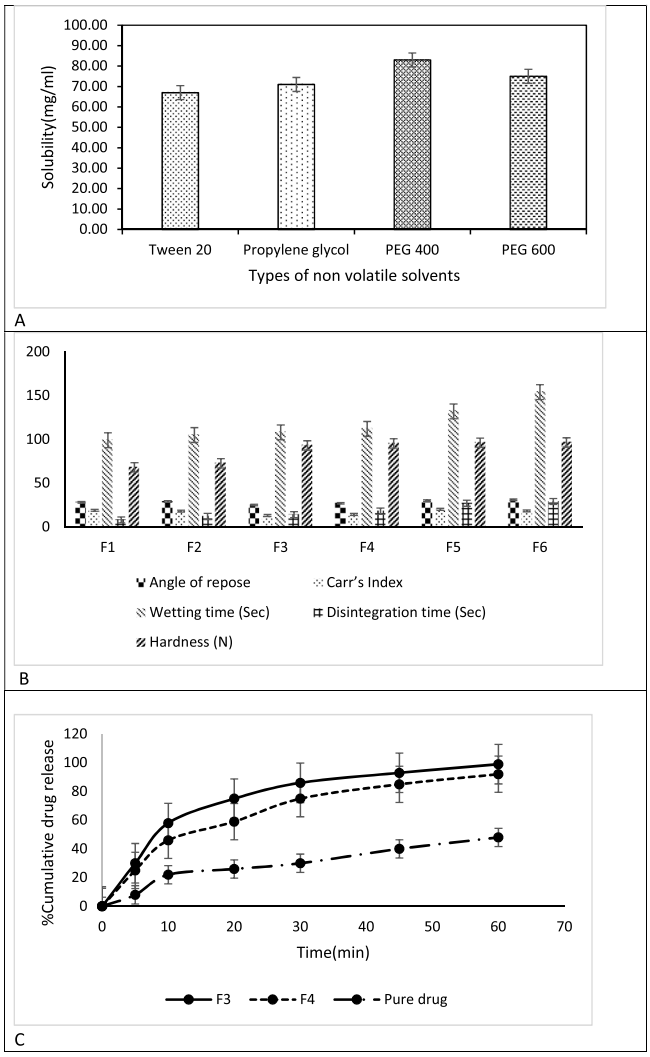

Fig. 2. Evaluation of tabletability of liquisolid compacts (A) and comparative dissolution study(B).

calculated using the formula[8].

$$DE = \frac{AUC_{0-60min}}{Q_{100}.T}100$$

Where $AUC_{0-60min}$ represents the area under the curve from the initial time to 60 min, T represents the total time of drug release and Q_{100} indicates 100 % drug release.

Differential scanning calorimetry (DSC Study)

Pure drug and the best formulation were weighed approximately 4 mg and placed in an Aluminium crucible and heated at a rate of 10 °C/min on a DSC 60 plus model (Shimadzu) from room temperature to 200 °C.

Powder X ray diffraction

The diffraction patterns of the pure drug and the best compact were generated using Malvern Panalytical X Pert 3 diffractometer. A scan at 2θ between 5 and 80° with a scan rate of 4°/min at Generator Settings of 30 mA, and 40 kV.

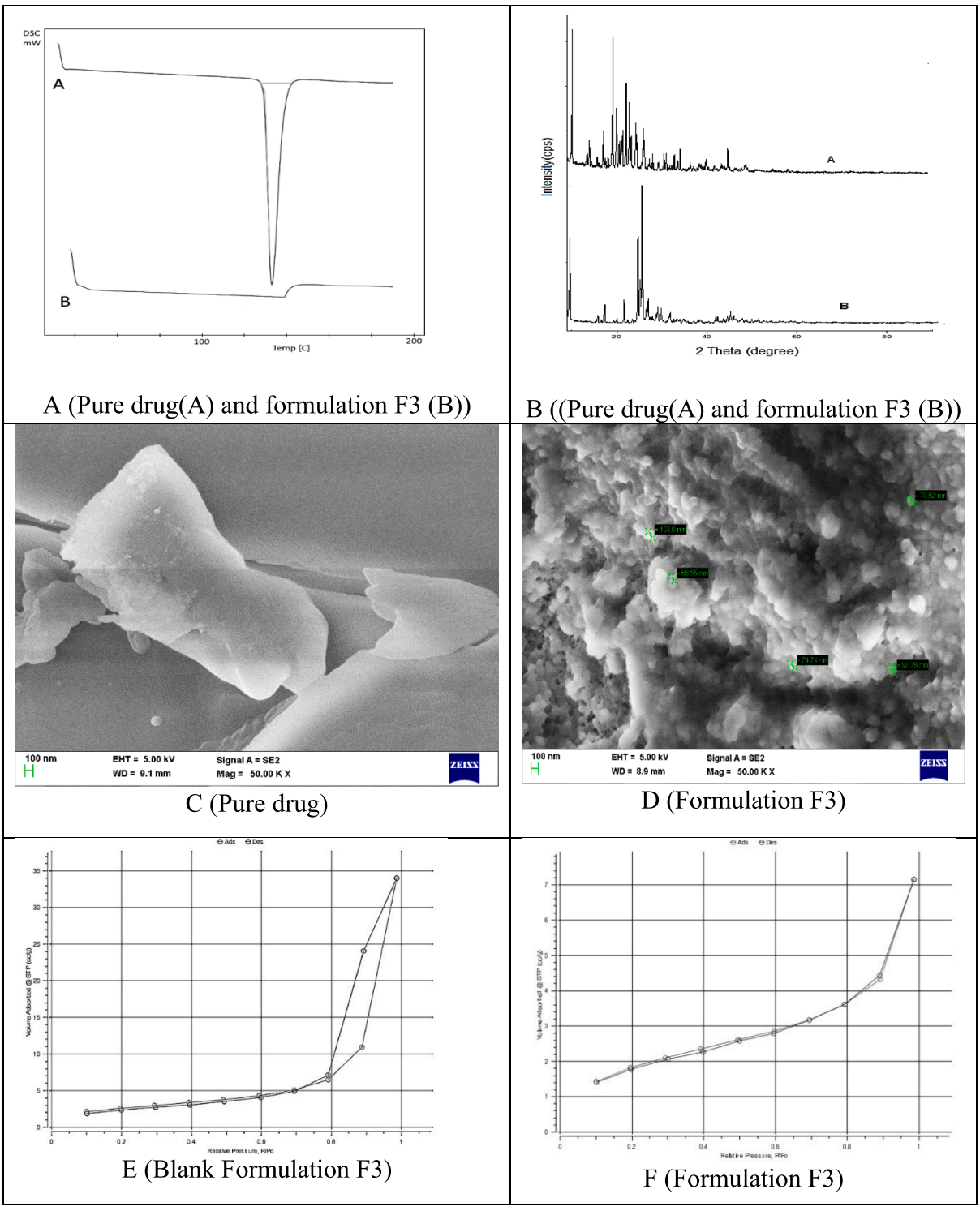

Fig. 3. DSC thermograms (A), PXRD patterns, SEM (C and D) and Surface area analysis (E,F).

Particle size determination

The particle size of the pure drug and the formulations were measured using Laser diffraction techniques (Shimadzu, Japan).

Surface morphology study

Surface morphology study was carried out using Zeiss, ultra 55 GEMINI® technology, sputter- coated samples were scanned at 5 kV.

Brunauer-Emmett- teller (BET)study

BET study was carried out on NOVA touch 1LX. The desorption and absorption study of the blank and drug loaded sample of F3 was carried out at nitrogen atmosphere at a bath temperature of 77.35 K with a cross sectional area of 16.2 $Å^2$/molec, for 51 min [9].

Results and discussion

The solubility of lumefantrine in different non-aqueous vehicles is presented in Fig. 2A.

Maximum solubility was achieved in PEG400, hence, it was selected as a non-volatile solvent for the preparation of liquisolid compact.

The liquisolid compacts of the six formulations were evaluated for angle of repose, and Carr's index and the observations are presented in Fig. 2B. It was observed that the flow property was good for all the formulations, but among them, formulations F3 and F4 showed good flow properties and compressibility.

The wetting time was found to be less for formulations with a high proportion of highly porous Syloid in the formulation. The hardness was found to be less, and friability was recorded more for tablets with a high proportion of Syloid. This might be due to the increased porosity of the liquisolid compact which resulted in high hardness and friability. The presence of mesoporous silica absorbs water into the tablet, creates expansion in the volume, and generates hydrostatic pressure required to provide rapid disintegration of the tablets. Hence the tablets with low wetting time exhibited fast disintegration.

The statistical evaluation of the properties of the liquisolid compact tablets of lumefantrine was done with Bonferroni's test at a significance level of $p < 0.05$ disclosed that all the formulations were found to be significantly different. It was identified that among all the formulations, the formulations F3 and F4 had good tableting properties (Carr's index < 15) with less disintegration time (<20 *sec*), good hardness (F3-93.11 N, F4-95.33 N), and less friability (F3-0.63 %, F4-0.67 %). Hence these two formulations were taken for the drug release study.

The comparative dissolution graphs of the two selected formulations (F3 and F4) and pure drug are shown in Fig. 2C. From the drug release study, it was found that the formulation F3 (particle size 100 nm) reached the asymptote at 60 min, whereas the formulation F4 (particle size 150 nm) and pure drug (particle size 876 nm) released 92 % drug and 48 % at 60 min respectively.

The dissolution efficiency ($AUC_{0-60min}$) was found to be 75.79.11 %, 66.25 %, and 30.91 % for F3, F4, and pure drug respectively. Comparing the drug release study, formulation F3 was considered the best among all and was subjected to further evaluation.

The thermal study (Fig. 3A) revealed that the pure drug exhibited a broad endothermic peak at 132 °C corresponding to the melting point, indicating its crystalline nature. The peak for the drug in formulation F3 was completely absent, which stipulated the conversion of the drug into its amorphous form. The PXRD study also revealed (Fig. 3B) the conversion of the drug to its amorphous form and hence, the enmeshment of the drug in the pores of Syloid 244FP resulted in enhancement of solubility and dissolution of the drug.

The surface morphology of the crystalline pure drug and the formulation F3 is shown in Fig. 3 (C and D). The surface morphology study of the pure drug revealed the crystalline nature of the drug, whereas the formulation F3 showed the entrapment of the drug in the nanopores of mesoporous silica.

The desorption and adsorption surface area of the formulation F3 was found to be 2.77114 m^2/g and 6.89112 m^2/g respectively, whereas the same for the blank sample was 11.7815 m^2/g and 9.45342 m^2/g respectively. The isotherm (Fig. 3E and 3F) exhibits a type IV curve, which is indicative of physisorption. The formulation F3 exhibited lower surface area and pore volume than the blank formulation, which proves the loading of the drug in the nanopores of the silica.

Conclusion

The present study intended to improve the dissolution of lumefantrine by formulation of a liquisolid compact of drug with a novel adsorbent of mesoporous silica. Experimental trials were carried out by varying the excipient ratio to attain the objective of the study. The tableting property was remarkably affected by the proportion of syloid in the formulation. A higher proportion has resulted in a friable tablet. The proportion of lactose as the carrier and syloid 244FP as the coating was found to be the best at an excipient ratio of 20. The thermal, surface characteristics, and surface area analysis study proved the amorphization of the drug in the nanopores of silica. The same observations were manifested in the surface morphology study. A comparative dissolution study indicated that the formulated liquisolid compact had better dissolution efficiency than the pure drug. Hence it can be concluded that liquisolid compact of lumefantrine in mesoporous silica can be an optimistic and effortless way to improve the dissolution of the drug.

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CRediT authorship contribution statement

Sayani Bhattacharyya: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Daivanai Ramachandran:** Investigation, Writing – review & editing, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mlblux.2022.100171.

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