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Lumefantrine Solid Dispersion Formulation Development and Characterization with Piperine for Solubility Enhancement

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A B S T R A C T

Lumefantrine's limited water solubility and variable bioavailability are linked to its crystallinity and efflux mediated by P-glycoprotein (P-gp). Here, amorphous solid dispersions (SD) of lumefantrine (LUMF) including piperine (PIP), a P-gp and CYP3A4 inhibitor, were produced using Copovidone/Kollidon® VA 64 (KOL) at three different ratios with increasing polymer content in order to increase the dissolution and, therefore, the oral bioavailability. Using DSC, FTIR, and XRD, the PIP-LUMF-KOL SD at a ratio of 1:6:18 showed increased aqueous solubility of LUMF. While FTIR tests looked into potential intermolecular interactions between LUMF and PIP and/or KOL, the DSC thermogram and XRD diffractogram of LUMF-PIP-SD validated the enhanced dissolving brought on by LUMF's loss of crystallinity. The stability of LUMFPIP-Sol SD under stressful temperature and humidity conditions for 90 days was confirmed by DSC and dissolving studies. Overall, the findings point to the possibility that increasing the SD of LUMF combined with P-gp inhibitor PIP may improve solubility and, in turn, increase LUMF's bioavailability.

Introduction

The biopharmaceuticals class II lumefantrine (LUMF), an antimalarial crystalline molecule, has limited water solubility and low/variable oral bioavailability (4-5%).[1-3] Because of its poor solubility in water, active efflux caused by the ATP-dependent efflux protein P-gp, and metabolic inactivation caused by CYP3A4, LUMF has a limited bioavailability.[4] Various approaches have been investigated to enhance the water solubility and oral bioavailability of LUMF. These include wet nano-milling, self-nano-emulsification, pheroid, pro-pheroid, and pheroid-emulsification. Nevertheless, the intricacy of these methods restricts their use.

Solid dispersions (SD) are extensively used to overcome the lattice energy limitations of crystalline drugs, hence increasing solubility and oral bioavailability.

By dissolving weakly watersoluble drugs in hydrophilic or amphiphilic carriers, the SD process transforms crystalline substances into amorphous ones.[7] Higher free energy combined with an amorphous form is thought to be responsible for the increase in apparent solubility, dissolving rate, and bioavailability.[8–11] The carrier polymer in SD prevents the thermodynamically unstable transition of an amorphous system to a stable crystalline state. This is done primarily through ant plasticization, specific drug–polymer interactions, reduced molecular mobility, energy barrier for crystal nucleation, and other mechanisms.[17] While a number of techniques, including as spray drying, hot melt extrusion, solvent evaporation, anti-solvent precipitation, freeze drying, and hot melt extrusion, have been used to synthesize SD, their primary disadvantages are the costly equipment and complex procedures they need. If toxicity or physical instability brought on by fast recrystallization, linked to ant solvent precipitation, solvent evaporation, and spray

drying processes, are involved, controlling leftover solvent may be difficult.[22] Contrarily, melting is an easy, affordable, solvent-free, and ecologically benign process.[23]

Solubility is a crucial component in assessing oral absorption since the drug candidate must be in an aqueous solution at the location prior to absorption.[24, 25] After oral administration of a poorly water-soluble medication, significant doses are required to achieve therapeutic concentration in the systemic circulation.[25] Two characteristics that influence a drug's oral bioavailability are permeability and propensity to be a P-gp substrate.[26] P-gp is an ATP-dependent efflux transporter that releases one drug molecule every cycle in addition to two ATP molecules being hydrolyzed.[27, 28] By competing for ATP binding sites on transporter protein, piperine (PIP) obstructs ATP hydrolysis and inhibits both CYP3A4 and P-gp.[29–32] It increases retention and impairs medication efflux via the gut.The restricted and irregular bioavailability of LUMF is also caused by P-gp's active efflux throughout the gut [31].The current investigation used an SD formulation including P-gp and the CYP3A4 inhibitor PIP to increase the LUMF's water solubility, which in turn improved the drug's intestinal absorption and oral bioavailability. Using the simple fusion/Co-melt process, Kollidon VA 64 (KOL) was used as a polymeric carrier to create the LUMF-SD. Physicochemical tests, such as Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and differential scanning calorimetry (DSC), were used to confirm the synthesis of SD.

Materials and Methods

Materials

BASF (KOL, Ludwigshafen, Germany); LUMF (Cipla Ltd., Aurangabad, India); Kollidon VA 64 (KOL). The supplier of PIP was Bio-Med Ingredients in Goa, India. The remaining chemicals were all analytical/HPLC grade (Merck, India).

Getting SD Ready

In order to achieve uniform dispersion, the appropriate amounts (Table 1) of LUMF and PIP were melted and added to the previously molten carrier (KOL) in a porcelain dish that was set on a hot plate while being continuously stirred. The temperature was maintained at 110 °C, which is greater than the KOL's Tg. The resulting dispersion was allowed to cool in an ice bath before being kept for a full day in a desiccator. After that, the dispersion was ground using a pestle and mortar and run through mesh number thirty. Following their blending, the physical mixes of LUMF-PIP and LUMF-PIP-KOL were sieved through mesh 30 and triturated in a mortar using a pestle.

Solubility at Saturation

0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and distilled water were used to measure the saturation solubility of LUMF-SD. In short, 100 mL of distilled water, 0.1 N HCl (pH 1.2), or phosphate buffer (pH 6.8) were combined with 100 mg of LUMF and SD in separate beakers. The mixture was then stirred at 100 rpm for a whole day at room temperature (1MLH, Remi Instruments, Mumbai, India).

Dissolution Research

In separate containers, 100 mL of distilled water, 0.1 N HCl (pH 1.2), and phosphate buffer (pH 6.8) were used for the dissolution experiments. LUMF and SD samples (100 mg) were added to containers holding dissolving medium that were continuously stirred at 100 rpm (1MLH, Remi Instruments, Mumbai, India) and maintained at 37°C. At a prearranged interval, samples were taken out, filtered through a 0.45 μm nylon syringe filter (J-Sil Scientific Industries, Agra, India), and then LUMF measurement was performed using an HPLC technique that has been verified. The Jasco PU2080 plus pumps with PDA detector and autosampler unit were part of the HPLC system that was used. With a stationary phase comprising a Hypersil C18 column (150 mm × 3.9 mm, 5 μm) and a mobile phase of acetonitrile and ammonium dihydrogen phosphate buffer (70:30 v/v) at a flow rate of 1 mL/min, the LUMF emitted was measured. The detector wavelength was set at 254 nm. Further analysis was done on the LUMF with the maximum aqueous solubility and dissolution, which were determined from LUMF-SD produced with PIP:LUMF:KOL (1: 6: 18).

Thermal study of crystalline medicines (LUMF and PIP), KOL, LUMF-PIP physical mixture, LUMF-PIP-KOL physical mixture, and L UMF-SD were performed using a D SC 6 0 (Shimadzu, Japan). The SD was characterized

using differential scanning calorimetry (DSC). In order to calculate the melting and glass transition temperatures (Tm and Tg), 5–10 mg of the sample was encapsulated in an aluminum plate and heated between 25 and 300°C at a rate of 10°C/min under a stream of nitrogen (50 mL/min).

Table 1: Composition of Formulations

Formulation	*PIP*	*LUMF*	*Polymer*
	1	6	6
PIP + LUMF + KOL	1	6	12
	1	6	18

Physical Stability

After 90 days of accelerated storage at 40°C/75% RH, the LUMF-SD was examined to ascertain the stability of LUMF in SD. The aged SD underwent a dissolution evaluation and DSC after 90 days. The dissolution of LUMF-SD was assessed in a jacketed beaker at 37°C with constant stirring (100 rpm) under non-sink circumstances. In summary, 100 mg of precisely weighed LUMF-SD was added to 100 mL of pH 6.8 phosphate buffer. Samples (1 mL) were taken out at prearranged intervals, filtered through a 0.45 µm nylon syringe filter, and the LUMF concentration was measured using HPLC. The influence of strained circumstances on the physical stability of LUMF in SD was ascertained by a comparison of the dissolution profiles and DSC thermograms of aged LUMF-SD (day 90) with LUMF-SD (Day 0).

Analytical Statistics

The collected data were presented as mean ± SD and subjected to One Way ANOVA analysis; statistical significance was defined as $p<0.05$.

Results and Discussion

Formulation and Solubility

While PIP, a P-gp inhibitor, has a limited bioavailability and solubility, concomitant dosing of PIP may improve the poor and variable bioavailability of LUMF.

Drug formulation as an SD that uses the right polymer or polymers may improve the drug's solubility, bioavailability, and bioenhancer. Additionally, improved pharmacokinetics and bioavailability of LUMF from SD have been demonstrated by Jain et al. (2017).[33] PIP is a suggested bioenhancer that is added to the formulation at a rate of around 10% w/w of the medication.[34] On the other hand, PIP's solubility and bioavailability were enhanced over SD made using KOL as a polymer in a 1:4 to 1:16 ratio.[35]

Furthermore, it was discovered that KOL improved the solubility and rate of LUMF's dissolution from SD in the ratio of 1:1 to 1:3 (LUMF:KOL).[36] Because LUMF can form glass well, it may be a suitable option for synthesizing amorphous silicon dioxide that is stable against crystallization using the fusion process.[19] Thus, in order to create LUMF-SD using the melt technique, the ratios of 1:6:6, 1:6:12, and 1:6:18 (PIP:LUMF:KOL) were selected for the current investigation. SD increases a dispersed drug's solubility by reaching supersaturation (Lim et al., 2015). There is more free drug available in the solution for absorption when the drug concentration in the solution surpasses the drug's solubility under supersaturation circumstances. The maximal solubility of pure LUMF in phosphate buffer pH 6.8 was found to be 69.36 ± 6.13 µg/mL, according to saturation solubility tests.

Dissolution Research

The dissolving curves of the LUMF and SD samples at different times in distilled water, 0.1 N HCl (pH 1.2), and phosphate buffer (pH 6.8) in the absence of a sink are shown in Fig. 2. In distilled water, LUMF, the pure medication, dissolved the slowest and had the lowest final concentration of 38.36 ± 12.91 µg/mL. LUMF-SD produced with KOL at a ratio of 1:6:18 (Fig. 1A) showed a faster and greater drug release after 8 hours in distilled water, with a final concentration of 316.22 ± 22.51 µg/mL. After 8 hours, 118.27 ± 28.40 (Fig. 1B) and 153.15 ± 53.50 µg/mL (Fig. 1C) of LUMF were released by the KOL containing LUMF-SD (1:6:18) in 0.1 N HCl (pH 1.2) and phosphate buffer (pH

6.8), respectively. It was discovered that when the polymer content in the SD rose, so did the rate and extent of dissolution in all three mediums. Higher surface free energy is available in the amorphous state than in the crystalline form.

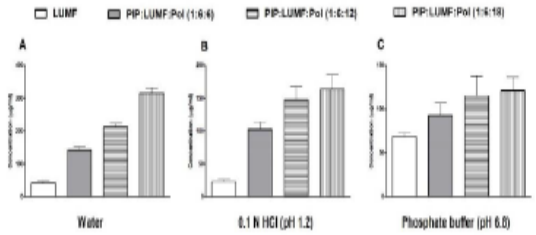

Fig. 1: Saturation solubility of LUMF alone and LUMF SD prepared with different ratios of KOL, in (A) water, (B) 0.1 N HCL (pH 1.2) and (C) phosphate buffer (pH 6.8).

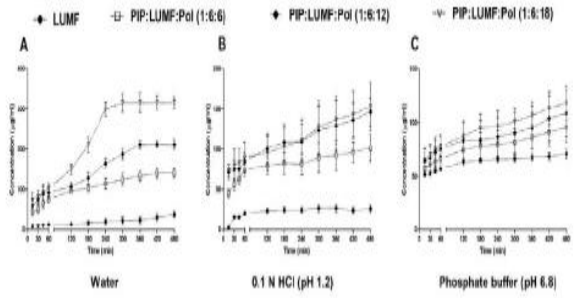

Fig. 2: Dissolution profiles of LUMF alone and LUMF SD prepared with different ratios of KOL, in (A) water, (B) 0.1 N HCL (pH 1.2) and (C) phosphate buffer (pH 6.8).

increasing a drug's solubility in its amorphous state.[37] Unlike crystalline form, the medication in an amorphous SD system does not need to cross the lattice energy barrier in order to dissolve since short-range intermolecular interactions are present.38 Consequently, the amorphous form that LUMF achieved in SD may be responsible for its enhanced saturation solubility and dissolution in SD. The SD with the largest amount of polymeric carrier showed the maximum LUMF saturation solubility and dissolving in all media, indicating that higher polymer content improves solubility and improves drug dissolution behavior. The PIPLUMF–KOL SD ratio of 1:6:18 demonstrated maximal drug release and solubility in an aqueous solution and may help increase LUMF's bioavailability; for this reason, it was taken into consideration and further studied.

DSC

Fig. 3 displays the DSC thermographs of LUMF, PIP, KOL, physical mixtures of LUMF: PIP, LUMF-PIP-KOL, and PIP: LUMF: KOL (1:6:18) SD. The enthalpies of 144.4 and 48.8 J/g, respectively, at the abrupt endothermic peaks at 141.9 and 133.5°C, respectively, indicated the crystalline nature of LUMF (Fig. 3A), PIP (Fig. 3B), and KOL (Fig. 3C). In comparison to that of LUMF or PIP, the DSC thermogram of the physical combination of PIP-LUMF (1:6) showed a protracted eutectic endothermic event of less energy (9.7 J/g) at 108.2°C earlier (Fig. 3D). The physical combination with KOL (Fig. 3E) showed no melting endotherm for either LUMF or PIP in the DSC thermogram, suggesting that the medicines might dissolve by heating in the hot, molten polymer. The polymer's Tg shifted to a lower temperature in the PIP:LUMF:KOL SD thermogram, exhibiting a broad, moderate endothermic event without any drug-specific melting endotherm, indicating that the medicines amorphized during melting (Fig. 3F). The stability of the amorphous drug in SD is shown by the single depressed Tg recorded during the second DSC run of the PIPLUMF-KOL physical mixture (Fig. 3F) and SD (Fig. 3H). This observation supports the creation of a single phase of medicines with polymer during the first run[39]. To ascertain the change in crystallinity, XRD XR D was used. The crystalline form of LUMF was revealed by the strong diffraction peaks at 2θ of 11.09, 13.49, 14.93, 18.04, 18.50, 19.11, 20.93, 21.51, 23.01, 28.18, and 31.97°, as shown in Fig. 4A. As shown in Figure 4B, the distinctive crystalline

strong peaks of PIP were detected at 2θ values of 14.67, 19.55, 22.55, 25.78, and 28.19°. In the diffractogram of the physical combination of LUMF and PIP, the decreased intensity of the diffraction peaks indicates the partial loss of

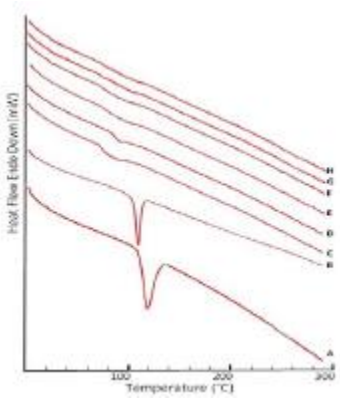

Fig. 3: DSC thermographs of A) LUMF, B) PIP, C) KOL, D) physical mixture of LUMF:PIP, E) physical mixture of LUMF:PIP:KOL, F) physical mixture of LUMF:PIP:KOL (Second Cycle), G) PIP:LUMF:KOL SD, H) PIP:LUMF:KOL SD (Second Cycle).

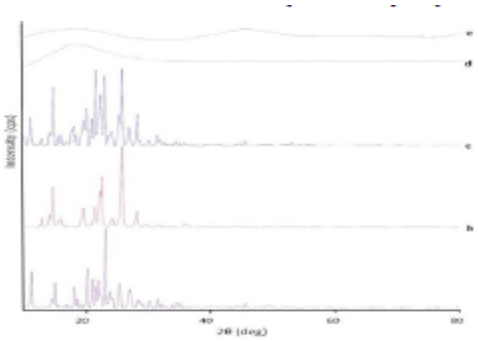

Fig. 4: XRD diffractogram of a) LUMF, b) PIP, c) physical mixture of LUMF:PIP, d) KOL and e) PIP: LUMF: KOL SD.

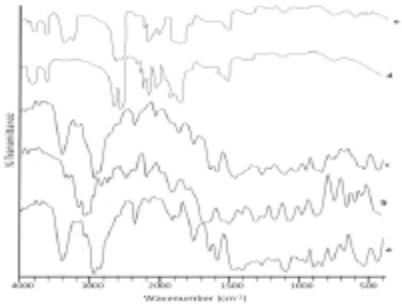

Fig. 5: FTIR spectra of a) LUMF, b) PIP, c) physical mixture of LUMFPIP, d) KOL, e) PIP-LUMF-KOL SD.

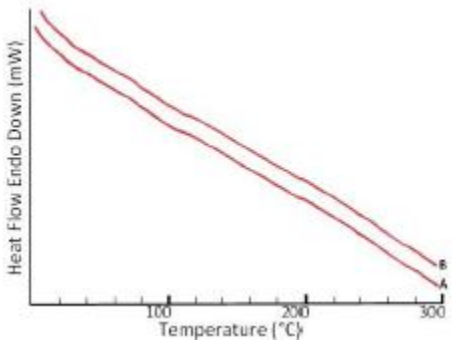

Fig. 6: DSC thermographs of LUMF- SD on day 0 (A) and day 90 (B). (LUMF-SD stored at stressed condition of 40 °C /75% RH.

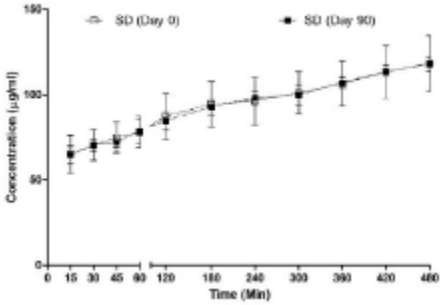

Fig. 7: LUMF-SD's dissolution profiles on days 0 and 90 (when it was kept in stressful circumstances at 40°C and 75% relative humidity). medication crystallinity (Fig. 4C). Furthermore, the lack of distinctive crystalline peak intensities for PIP and LUMF in SD shows that the medicines are in an amorphous form (Fig. 4E).
The XRD tests support the amorphous form of PIP:LUMF:KOL in SD, which is responsible for the improved aqueous solubility of LUMF in SD.

Conclusion

It was discovered that the LUMF's aqueous solubility, extent, and rate of dissolution from SD containing KOL had improved. It was previously believed that following storage under stressful settings, the amorphous form of LUMF in SD would be preserved via the molecular interactions between medicines and polymer. Overall, the study indicates that SD co-loaded with P-gp inhibitor can be used as a workable formulation strategy to enhance LUMF's aqueous solubility and bioavailability, which could enhance the drug's effective delivery and maximize its therapeutic benefits in conjunction with dose and/or frequency reduction.

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