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FORMULATION DEVELOPMENT OF PVP-BASED SOLID DISPERSION OF LUMEFANTRINE WITH PIPERINE FOR SOLUBILITY ENHANCEMENT

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ABSTRACT: The oral bioavailability of lumefantrine (LUMF) is low and erratic owing to its low aqueous solubility and P-glycoprotein (P-gp) mediated efflux. The present investigation aims to develop amorphous solid dispersions (SD) of LUMF co-loaded with piperine (PIP), a P-gp and CYP3A4 inhibitor, to improve its dissolution and thereby oral bioavailability. LUMF-SDs were prepared by using Polyvinyl-pyrrolidone, grade Povidone K30 (PVP) as a polymeric carrier, at three different ratios with increasing concentrations of polymer, employing melt method. DSC, XRD and FTIR characterized the PIP-LUMF-PVPSD at ratio of 1:6:18demonstrating higher aqueous solubility of LUMF. The DSC thermogram and XRD diffractogram confirmed the loss of crystallinity of both LUMF and PIP in PIP-LUMF SD, resulting in improved dissolution. Moreover, the possible molecular interactions between LUMF and PIP and /or PVP were investigated by FTIR studies. Crystallinity being a function of time, the stability of LUMF-PIP-PVP SD exposed to stressed humidity and temperature conditions (40 °C/75% RH) for 90 days was validated by DSC and release studies. These findings suggest that the SD of LUMF incorporated with P-gp inhibitor PIP improves dissolution and thereby could improve the bioavailability of LUMF.

INTRODUCTION: Lumefantrine (LUMF), a first-line crystalline antimalarial agent, is a Biopharmaceutics Classification System class II drug with pooraqueous solubility and low oral bioavailability [1-3]. Low and inconsistent bioavailability (4 – 11%) of LUMF stems from its low aqueous solubility, active efflux by P-gp (ATP-dependent efflux protein), and metabolic inactivation by CYP3A4 [4].

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Several approaches have been employed to improve aqueous solubility and oral bioavailability of LUMF including wet nano-milling [5], self-nano-emulsification [2], pheroid [6] and pro-pheroid [1]. However, aforementioned techniques are associated with drawbacks of complex procedures and expensive formulation development which limits their applicability.

The amorphous form of crystalline drug in solid dispersions (SD) has been utilized to improve solubility and oral bioavailability by overcoming the constraints of lattice energy of crystalline drug. Solid dispersion aids the conversion of crystalline state into an amorphous by offering the dissolution of the poorly water-soluble drug in a hydrophilic or

amphiphilic carrier [7]. The amorphous state of drug exhibits higher apparent solubility, dissolution rate, and bioavailability due to greater free energy [8-11]. The thermodynamically unstable transition of an amorphous system to a stable crystalline state is avoided by the carrier polymer in SD [12, 13], which is accomplished mainly through antiplasticization [14], specific intermolecular interactions between drug and polymer [15], reduced molecular mobility [16], and energy barrier for crystal nucleation [17]. While several strategies have been used to synthesize SD, including spray drying, hot melt extrusion [18], solvent evaporation [19], anti-solvent precipitation [20], and freeze drying [21], their main drawbacks are the expensive equipment and intricate processes they require. Controlling residual solvent might be challenging if toxicity or physical instability triggered by accelerated recrystallization, associated with anti-solvent precipitation, solvent evaporation and spray drying techniques, are involved [22]. Per contra, melting is a simple, solvent-free, inexpensive, and environmentally friendly method [23].

Poor aqueous solubility of a drug is a key factor in attaining therapeutic concentration in systemic circulation since the drug candidate needs to be in aqueous solution at the site before absorption [24, 25]. Therefore, oral absorption of poorly water-soluble drugs necessitates high doses to attain therapeutic concentration [25]. Moreover, permeability and tendency to be a P-gp substrate determine the oral bioavailability of a drug [26]. P-gp is an ATP-dependent efflux transporter and it expels one molecule of absorbed drug per cycle along with hydrolysis of two ATP [27, 28]. Piperine (PIP) interferes with ATP hydrolysis by vying for ATP binding sites on transporter protein, inhibiting both CYP3A4 and P-gp [29-32].

It hampers the drug efflux across the intestine and augments retention [31]. Active efflux by P-gp across the intestine also contributes to the limited and erratic bioavailability of LUMF33 [4]. Present study aimed to enhance aqueous solubility to improve oral bioavailability and intestinal absorption of LUMF using SD formulation incorporated with P-gp and CYP3A4 inhibitor, PIP. The LUMF-SD was synthesized by incorporating polyvinyl pyrrolidone K30 (PVP) as a polymeric carrier, employing a simple melt/ fusion method.

The formation of SD was confirmed by physicochemical analyses, including differential scanning calorimetry (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR).

MATERIALS AND METHODS:

Chemicals: Polyvinyl pyrrolidone, grade Povidone K30 (Kollidone ®30-BASF, Ludwigshafen, Germany), Lumefantrine (Cipla Ltd., Aurangabad, India). Piperine was purchased from Bio-Med Ingredients (Goa, India). All the other chemicals and solvents used were of HPLC (Merck, India)/ analytical grade.

Preparation of SD: Lumefantrine SD was prepared by melt method; appropriate quantities **Table 1** of LUMF and PIP were melted by adding to previously molten carrier (PVP), in a porcelain dish placed on a hot plate under continuous stirring to produce homogenous dispersion. The melting process was carried out at a temperature of 130±5°C. The resultant dispersion was cooled in an ice bath and stored in a desiccator for 24 h. The dispersion was then pulverized in a mortar with a pestle and passed through mesh 30. The physical mixtures of LUMF-PIP and LUMF-PIP-PVP were prepared by blending the drugs in a mortar with a pestle and then sieved through mesh 30.

TABLE 1: COMPOSITION OF SD FORMULATIONS

Formulation code	Drug -Polymer Ratio		
	PIP	LUMF	PVP
F1	0.167	1	1
F2	0.167	1	2
F3	0.167	1	3

Saturation Solubility: Saturation solubility was evaluated in distilled water, 0.1 N HCl (pH 1.2), and phosphate buffer (pH 6.8). In brief, 100 mg of LUMF and SD were added to separate beakers containing 100 ml of distilled water, 0.1 N HCl (pH 1.2), or phosphate buffer (pH 6.8), and the mixture was agitated at 100 rpm for 24 h at room temperature (1MLH, Remi Instruments, Mumbai, India). Samples were withdrawn after 24 h were filtered through nylon syringe filter (0.45 μm) and analyzed for LUMF content.

Dissolution Studies: The dissolution study of pure LUMF and SDs was performed in 100 ml each of distilled water, 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) contained in separate vessels.

LUMF and SD samples (100 mg) were added to the vessels containing dissolution media maintained at 37 °C and stirred at 100 rpm (1MLH, Remi Instruments, Mumbai, India). Samples were withdrawn at a predetermined interval, filtered through nylon syringe filter (0.45 µm; J-Sil Scientific Industries, Agra, India) and subjected to LUMF analysis using a validated HPLC method. The HPLC system was employed with Jasco PU2080 plus pumps, PDA detector, and autosampler unit. The LUMF released was quantified using Hypersil C18 column (150 mm × 3.9 mm, 5 µm) as the stationary phase, the mobile phase comprised of acetonitrile and ammonium dihydrogen phosphate buffer (70:30 v/v) at a flow rate of 1 ml/min and detector wavelength set at 254 nm. The highest aqueous solubility and dissolution for LUMF were estimated from LUMF-SD prepared with PIP: LUMF: PVP (1:6:18) and hence, were subjected for further characterization.

Characterization of SD:

Differential Scanning Calorimetry (DSC): Thermal analysis of crystalline drugs (LUMF and PIP), PVP, LUMF-PIP physical mixture, LUMF-PIP-PVP physical mixture, and LUMF-SD was performed using a DSC 60 (Shimadzu, Japan). For each analysis, approximately 5-10 mg of the sample was sealed in an aluminum plate and heated from 25°C to 300°C at a rate of 10°C/minunder a stream of nitrogen (50 ml/min) to determine melting (T_m) and the glass transition temperature (T_g).

X-ray Powder Diffractometry (XRD): A Rigaku Miniflex-600 Diffractometer equipped with Cu-Kα radiation source was used to record X-ray diffraction profiles of LUMF, PIP, LUMF-PIP physical mixture, PVP, and LUMF-SD. The diffraction patterns were recorded in the spectral range of 10-80° (2θ) using the Cu-target X-ray tube as an X-ray source, Xe filled detector with voltage 40 Kv and fixed current at 20 mA.

Fourier Transform Infrared Spectroscopy (FTIR): For FTIR analysis, the samples of LUMF, PIP, LUMF-PIP physical mixture, PVP, and LUMF-SD were prepared by mixing with dry potassium bromide using a mortar and pestle and compressed to pellet. The pellets were then scanned in the 4000 – 500 cm-1 spectral range using FTIR Spectrophotometer (IR affinity, Shimadzu, Japan).

Physical Stability: To determine the stability of LUMF in SD, the LUMF-SD was kept under accelerated storage conditions (40 °C /75% RH) for 90 days. After 90 days, the aged SD was subjected to DSC and dissolution assessment. The dissolution of LUMF-SD was evaluated under non-sink conditions at 37 °C in a jacketed beaker under continuous stirring (100 rpm). Briefly, accurately weighed 100 mg of LUMF-SD was introduced into phosphate buffer pH 6.8 (100 ml). At predetermined intervals, samples (1 ml) were withdrawn, filtered through a 0.45 µm nylon syringe filter, and analyzed by HPLC for LUMF concentration. The impact of stressed conditions on the physical stability of LUMF in SD was determined by comparing the DSC thermograms and dissolution profiles of aged LUMF-SD (day 90) were compared LUMF-SD (Day 0).

RESULTS AND DISCUSSION:

Formulation and Solubility: Concomitant administration of a P-gp inhibitor, PIP, can improve the poor and variable bioavailability of LUMF. However, PIP, too, has limited aqueous solubility and bioavailability. SD formulated with appropriate polymer/s can augment the solubility and bioavailability of the drug and the bioenhancer. Furthermore, the enhanced pharmacokinetics and bioavailability of LUMF from SD have been reported [33].

PIP concentration equivalent to approximately 10% w/w of the drug in the formulation is suggested to impart bioenhancing properties [34]. The rate and extent of PIP dissolution was improved from SD formulated with PVP as a polymer in the ratio 1:4 [35]. Moreover, PVP was found to enhance the solubility and dissolution rate of LUMF, in concentration-dependent manner, from SD in the ratio 1:0.2 to 1:2 (LUMF: PVP) [36]. The melt/fusion method appears to be suitable for preparing amorphous LUMF-SD, stable against crystallization since LUMF possesses good glass-forming ability [19]. Therefore, in the current investigation, the ratios of 1:6:6, 1:6:12 and 1:6:18 (PIP: LUMF: Polymer) were selected to prepare LUMF-SD by using melt method.

The solubility of the drug dispersed in the SD form is augmented by achieving supersaturation [37]. Under the conditions of supersaturation, higher amount of free drug is available in solution state for absorption since the concentration of drug in the solution surpasses its solubility. The maximum solubility (69.36 ± 6.13 µg/ml) of pure LUMF was displayed in phosphate buffer pH 6.8. After 24 h, the SDs prepared with increasing ratio of polymeric carrier exhibited enhanced LUMF solubility in aqueous, 0.1 N HCl (pH 1.2) as well as phosphate buffer (pH 6.8) medium. Therefore, the order of increase in LUMF solubility from SDs in all three media was F1<F2<F3. The highest solubility of LUMF from F3SD (1:6:18) was attained in distilled water (121.02 ± 14.00 µg/ml) **Fig. 1A** followed by 118.71 ± 24.25 µg/ml **Fig. 1C** in phosphate buffer (pH 6.8) and 108.36 ± 42.51 µg/ml **Fig. 1B** in acidic medium (0.1 N HCl pH 1.2). The aqueous saturation solubility for pure LUMF after 24 h was 42.14 ± 10.81 µg/ml, which increased in F3 SD (1:6:18) by 187 % (121.02 ± 14.00 µg/ml) **Fig. 1A**, indicating enhancement of LUMF aqueous solubility by PVP.

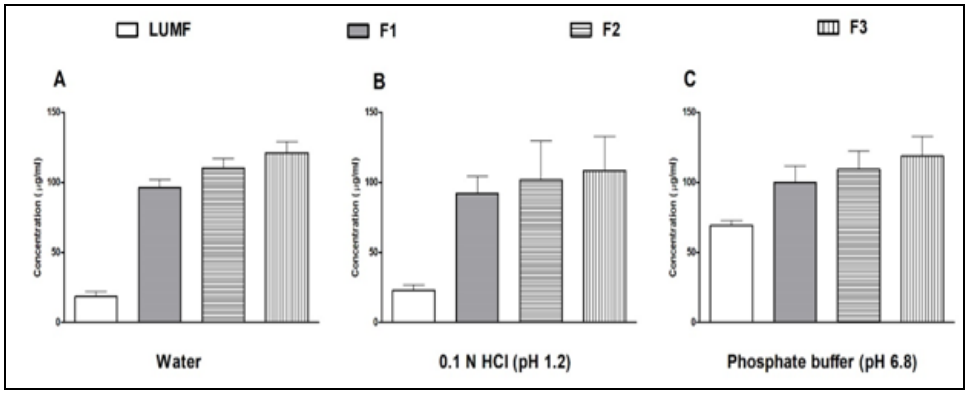

FIG. 1: SATURATION SOLUBILITY OF LUMF ALONE AND LUMF SD PREPARED WITH DIFFERENT RATIOS OF PVP, IN (A) WATER, (B) 0.1 N HCL (PH 1.2) AND (C) PHOSPHATE BUFFER (PH 6.8).

Dissolution Studies: Fig. 2 represents the dissolution profiles of LUMF and SD samples at different time points in distilled water, 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) under non-sink conditions. LUMF-SD composed of PVP at ratio 1:6:18 (F3) demonstrated higher rate and extent of drug release at 8 h in distilled water **Fig. 1A** with a final concentration of 121 ± 9.23 µg/ml. While, pure LUMF dissolved the slowest with the lowest final concentration of 38.36±12.91 µg/ml in distilled water. The F3 SD (1:6:18) demonstrated 105.78±42.56 µg/ml **Fig. 1B** and 115.47±25.55 µg/ml **Fig. 1C** of LUMF release in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8), respectively after 8 h.

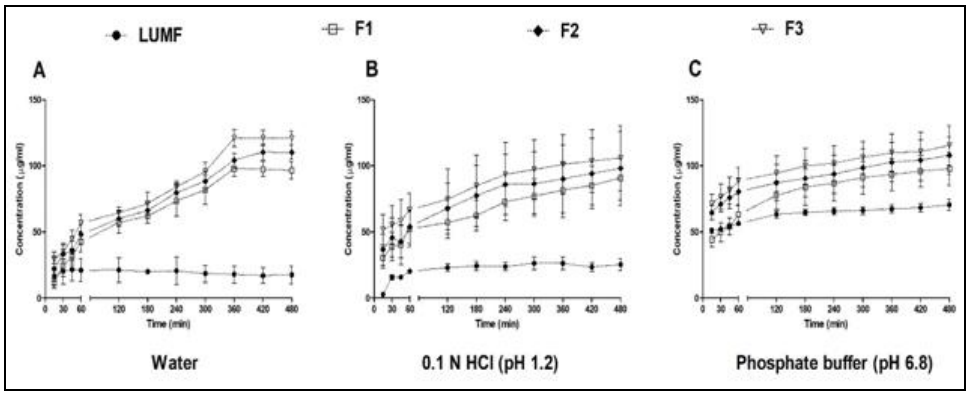

FIG. 2: DISSOLUTION PROFILES OF LUMF ALONE AND LUMF SD PREPARED WITH DIFFERENT RATIOS OF PVP, IN (A) WATER, (B) 0.1 N HCL (PH 1.2) AND (C) PHOSPHATE BUFFER (PH 6.8).

However, F1 (1:6:6) and F2 (1:6:12) SDs exhibited a lesser rate and extent of drug release compared to F3 (1:6:18) SD in all three media, indicating the rate, as well as the extent of dissolution in all three media, increased with increasing concentration of polymer in the SD. Higher surface free energy of

metastable amorphous form offers higher solubility than the stable crystalline form [38]. The lattice energy of the crystalline form hinders drug dissolution. Per contra, in amorphous SD, with short-range intermolecular interactions, the drug does not have to overcome such hindrance [39]. Therefore, the improvement observed in saturation solubility and dissolution of LUMF in SD could be ascribed to its amorphous state acquired in SD. Regardless of the medium, the saturation solubility and dissolution of LUMF were extreme in the SD composed of maximum polymer content (F3), suggesting that the enhancement of solubility and improved drug dissolution behavior is proportional to polymer concentration. The SD formulation F3 (PIP: LUMF: PVP-1: 6:18) showed maximum solubility and drug release in an aqueous medium and may contribute to the bioavailability enhancement of LUMF. Therefore, F3 SD was selected for further characterization.

DSC: DSC is widely used to investigate the miscibility of the drug with the polymeric carrier in the SD system and amorphous/crystalline behaviour of SD components [35, 40].

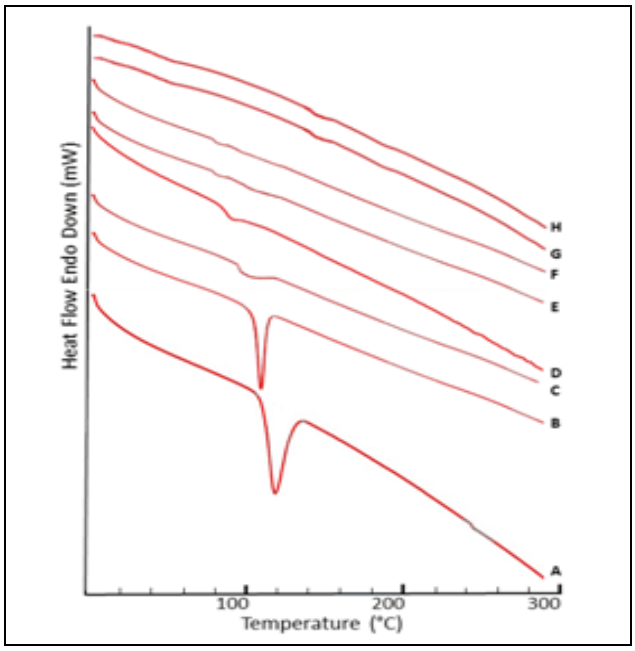

FIG. 3: DSC THERMOGRAMS OF A) LUMF, B) PIP, C) PVP, D) PHYSICAL MIXTURE OF LUMF: PIP, E) PHYSICAL MIXTURE OF LUMF: PIP: PVP, F) PHYSICAL MIXTURE OF LUMF: PIP: PVP (SECOND CYCLE), G) F3, H) F3 (SECOND CYCLE).

DSC thermograms of LUMF, PIP, PVP, physical mixture of LUMF-PIP, physical mixture of LUMF-PIP-PVP, and F3 SD are shown in **Fig. 3**. The sharp endothermic peaks at 141.9 °C **Fig. 3A** and 133.5 °C **Fig. 3B** with corresponding enthalpies of 144.4 J/g and 48.8 J/g demonstrated the crystalline nature of LUMF and PIP, respectively. An extended endothermic peak with less energy (9.7 J/g) at 108.2 °C, earlier to that of LUMF or PIP, in the DSC thermogram of the physical mixture of PIP- LUMF (1:6) **Fig. 3D** suggests the formation of eutectic mixture of LUMF with PIP. The possible dissolution of drugs (LUMF and PIP) in the hot molten polymer through heating was evident by the absence of melting endotherms of both LUMF and PIP in the DSC thermogram of their physical mixture with PVP **Fig. 3E**.

The shift of T_g of polymer to lower temperature, which appeared as a small and broad endothermic peak without any melting endotherm corresponding to either drug, suggests the amorphization of drugs during melting **Fig. 3F**.

A single enervated endothermic event detected in thermograms of the second DSC run of PIP-LUMF-PVP physical mixture **Fig. 3F** and SD **Fig. 3H** justify the formation of a single phase of drugs with the polymer during the first run (Chokshi *et al.*, 2007) and also stipulate the stability of amorphous drug in SD.

XRD: The X-ray diffraction technique is used to confirm the amorphous nature of the drug in SD by determining the change in crystallinity. As depicted in **Fig. 4A**, pure crystalline LUMF displayed the sharp 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°. Intense diffraction peaks at 2θ of 14.67, 19.55, 22.55, 25.78, and 28.19° **Fig. 4B** suggests the crystalline nature of PIP.

The decrease in intensity of diffraction peaks of the physical mixture of LUMF and PIP indicates the partial loss of crystallinity of drugs **Fig. 4C**. Moreover, the disappearance of characteristic crystalline peaks of LUMF and PIP in the diffractogram of F3 suggests amorphous state of drugs in SD **Fig. 4E**. XRD and DSC characterizations complement each other in confirming the amorphous nature of LUMF in SD. The increased aqueous solubility of LUMF in SD could be attributed to the amorphous nature of LUMF in SD.

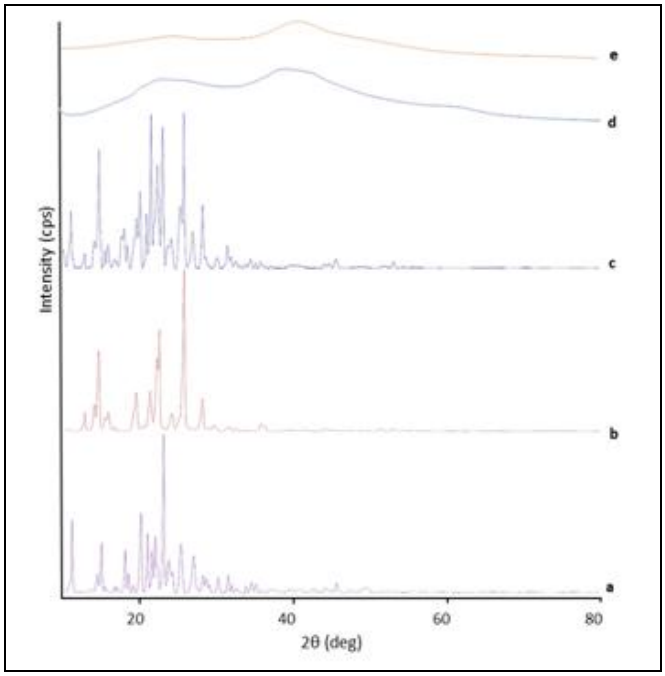

FIG. 4: XRD DIFFRACTOGRAMS OF A) LUMF, B) PIP, C) PHYSICAL MIXTURE OF LUMF: PIP, D) PVP, E) F3

FTIR: Possible interactions between the drugs and polymer in the physical mixture and SD were investigated by FTIR analysis. The spectra of LUMF, PIP, physical mixture of LUMF and PIP, PVP and SD (F3) are shown in **Fig. 5**. FTIR spectrum of LUMF **Fig. 5A** displayed the characteristic peaks at 3402 cm^{-1} (O-H stretching), 2947 cm^{-1} (C-H stretching), 1635 cm^{-1} (C=C alkene stretching), 1581 cm^{-1} (C=C aromatic stretching), 1087 cm^{-1} (C-N stretching), 1022 cm^{-1} (C-O stretching) and 520 cm^{-1} (C-Cl stretching). As depicted in **Fig. 5B**, PIP has characteristic peaks at 2935 cm^{-1} (C-H aromatic stretching), 2866 cm^{-1} (C-H aliphatic stretching), 1627 cm^{-1} (C=O stretching), 1261 cm^{-1} (-O-CH_2-O stretching) and 937 cm^{-1} (C-O stretching). The absence of a significant shift in characteristic peaks of either drug in the FTIR spectrum of the PIP-LUMF physical mixture (Figure 5C) suggested no chemical interaction occurred between LUMF and PIP.

FTIR spectrum of PVP displayed a C-H stretching band at 2925 cm^{-1} and stretching vibration of carbonyl group at 1653 cm^{-1}. Moreover, =N- and C=O groups of each pyrrolidone moiety of PVP can potentially form a hydrogen bond with the drug at the molecular level in the SD. The broad peaks at 3416 and 1695 observed in the spectrum of SD **Fig. 5E** suggested hydrogen bonding between the hydroxyl group of LUMF and carbonyl group of PVP [41]. The shift in carbonyl band of PIP from 1627 cm^{-1} to 1639 cm^{-1} in SD represents the hydrogen bonding between PIP and PVP. The hydrogen bonding between drugs and polymer could be a driving force in enhancing the miscibility favored by the molecular level distribution of drugs in SD system which could thus retard phase separation and recrystallization and facilitate the solubilization of drugs [15, 35, 40].

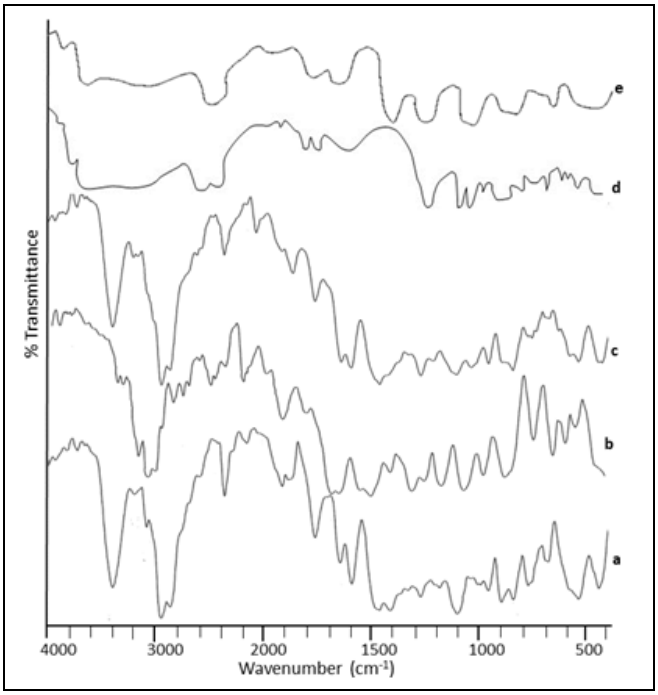

FIG. 5: FTIR SPECTRA OF A) LUMF, B) PIP, C) PHYSICAL MIXTURE OF LUMF-PIP, D) PVP, E) F3

Stability Studies: Being a thermodynamically metastable system SD has natural propensity to convert into a stable crystalline state from amorphous state and consequently may influence the solubility and dissolution behaviour. Physical stability of F3 was evaluated by DSC and dissolution studies after storage under stressed conditions. As depicted in **Fig. 6**, no significant difference in DSC. Thermograms of F3 stored at 40 °C /75% RH for 3 months and that of on day 0 was observed. Moreover, the similar dissolution profiles of aged (day 90) SD and fresh SD (day 0) evident the conservation of amorphous state of LUMF over 3 months of storage under stress conditions **Fig. 7**. Inhibition of molecular mobility and phase transition of SD owing to molecular interactions between drug and polymer, evident by FTIR studies, could be corroborated by the physical stability of F3 after storage under stress conditions.

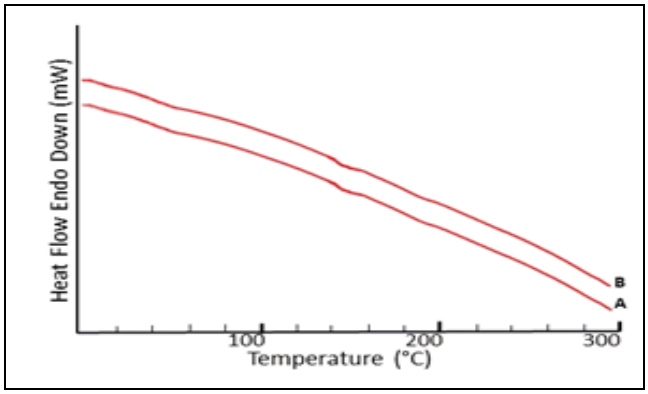

FIG. 6: DSC THERMOGRAMS OF F3 ON DAY 0 (A) AND DAY 90 (B) (F3 STORED AT STRESSED CONDITIONS OF 40 °C /75% RH).

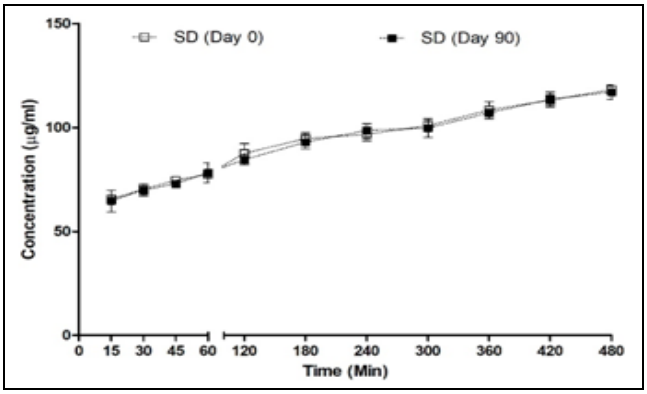

FIG. 7: DISSOLUTION PROFILES OF F3 ON DAY 0 AND DAY 90 (F3 STORED AT STRESSED CONDITIONS OF 40 °C/75% RH).

CONCLUSION: LUM's high degree of solubility enhancement contributes to the dissolution rate enhancement of LUM: PIP: PVP SD. The extent and rate of dissolution of LUMF from SD containing PVP were found to be improved in a concentration-dependent manner. The use of PVP polymer is feasible for melt application and production of fully amorphous solid dispersion.

The physical interactions between drugs and polymer at the molecular level were supposed to maintain the amorphous state of LUMF in SD after storage under stressed conditions. The study suggests LUMF SD using PVP & combined with PIP (P-gp inhibitor) can be immersed as a workable formulation design to enhance aqueous solubility and dissolution and thereby could improve bioavailability of LUMF.

CONFLICTS OF INTEREST: Authors report no potential conflicts of interest.

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