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Research Article

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

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ABSTRACT

Lumefantrine low/variable bioavailability with low aqueous solubility is associated with their crystallinity and P-glycoprotein (P-gp) mediated efflux. Herein, to improve the dissolution and hence the oral bioavailability, amorphous solid dispersions (SD) of lumefantrine (LUMF) containing piperine (PIP), a P-gp and CYP3A4 inhibitor, were prepared with Copovidone/Kollidon® VA 64 (KOL) at three different ratios with increasing content of the polymer. The PIP-LUMF-KOL SD at ratio of 1:6:18 demonstrated higher aqueous solubility of LUMF and hence were characterized by DSC, FTIR and XRD. The improved dissolution resulting due to loss of crystallinity of LUMF was confirmed by DSC thermogram and XRD diffractogram of LUMF-PIP-SD while FTIR studies investigated the possible intermolecular interactions between LUMF and PIP and /or KOL. DSC and dissolution experiments validated the stability of LUMF-PIP-Sol SD for 90 days under stressed humidity and temperature conditions. Overall, the data suggest that the SD of LUMF incorporated with P-gp inhibitor PIP, enhances dissolution and hence could improve the bioavailability of LUMF.

Introduction

Low water solubility and low/variable oral bioavailability (4–11%) characterize the antimalarial crystalline compound lumefantrine (LUMF) in the Biopharmaceutics Classification System class II.[1-3] LUMF has low bioavailability due to low aqueous solubility, active efflux by P-gp (ATP-dependent efflux protein) and metabolic inactivation by CYP3A4.[4] To improve aqueous solubility and oral bioavailability of LUMF, several strategies, including wet nano-milling,[5] self-nano-emulsification[2], pheroid[6] and pro-pheroid[1] have been explored. However, the complex procedures of these techniques limit their application.

Solid dispersions (SD) are widely being utilized to improve solubility and oral bioavailability by overcoming the constraints of lattice energy of crystalline drug. SD technique enables the dissolution of poorly water-soluble drug in hydrophilic or amphiphilic carrier, thus converting the crystalline substance into amorphous.[7] The augmentation of apparent solubility, dissolution rate and bioavailability are ascribed to higher free energy accompanied with an amorphous state.[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 for the synthesis of SD, including spray drying, hot melt extrusion,[18] solvent evaporation,[19] anti-solvent precipitation,[20] 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

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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]

Since the drug candidate needs to be in an aqueous solution at the site before absorption, solubility is a key factor in determining oral absorption.[24,25] Substantial dosages are necessary to attain therapeutic concentration in systemic circulation after oral administration of a poorly water-soluble drug.[25] Permeability and inclination to be a P-gp substrate are factors that affect a drug's oral bioavailability.[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 LUMF.[4] The 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 Kollidon VA 64 (KOL) as a polymeric carrier, employing simple fusion/Co-melt 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).

Solid dispersions convert a crystalline drug into an amorphous form, exhibiting higher solubility than its crystalline counterpart. Due to their low solubility and dissolution rate, water-insoluble drugs often suffer from limited absorption. LUMF efflux mediated by P-gp further reduce the available plasma level, leading to a higher dose requirement for therapeutic effect. Formulating a solid dispersion, the drug's solubility and dissolution properties can be optimized for augmented bioavailability which translates into more significant therapeutic effects and may reduce the required dosage or dosing frequency. The rational preparation of solid dispersions for water-insoluble and low bioavailable drugs aims to improve their solubility, dissolution rate, and bioavailability achieved by the inclusion of piperine, a P-gp efflux inhibitor. Dispersion of LUMF in a carrier matrix will expectedly enhance the drug's interaction with the surrounding fluid, increasing drug dissolution, absorption, and systemic exposure. These improvements contribute to the effective delivery of the drug and maximize its therapeutic outcomes.

Materials and Methods

Materials

Kollidon VA 64 (KOL, BASF, Ludwigshafen, Germany), LUMF (Cipla Ltd., Aurangabad, India). PIP was purchased from Bio-Med Ingredients (Goa, India). All the other chemicals used were of HPLC (Merck, India)/analytical grade.

Preparation of SD

Appropriate quantities (Table 1) of LUMF and PIP were melted by adding to the previously molten carrier (KOL), in a porcelain dish placed on a hot plate under continuous stirring to produce homogenous dispersion. The temperature was held at 110 °C (temperature higher than T_g of KOL). The resultant dispersion was cooled in an ice bath and stored in a desiccator for 24 hours. The dispersion was then milled in a mortar with a pestle and passed through mesh 30. After being blended, the physical mixtures of LUMF-PIP and LUMF-PIP-KOL were triturated in a mortar with a pestle and sieved through mesh 30.

Saturation Solubility

Distilled water, 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) were used to assess the saturation solubility of LUMF-SD. Briefly, 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 hours at room temperature (1MLH, Remi Instruments, Mumbai, India).

Dissolution Studies

Dissolution studies were performed using 100 mL each of distilled water, 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) placed in separate vessels. In vessels containing dissolution media kept at 37°C under continuous stirring at 100 rpm (1MLH, Remi Instruments, Mumbai, India), LUMF and SD samples (100 mg) were introduced. Samples were withdrawn at a predetermined interval, filtered through 0.45 µm nylon syringe filter (J-Sil Scientific Industries, Agra, India) and subjected to LUMF analysis using a validated HPLC method. The HPLC system employed was equipped with Jasco PU2080 plus pumps with 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 estimated from LUMF-SD prepared with PIP:LUMF:KOL (1: 6: 18) were further characterized.

Characterization of SD

Differential Scanning Calorimetry (DSC)

Thermal analysis of crystalline drugs (LUMF and PIP), KOL, LUMF-PIP physical mixture, LUMF-PIP-KOL 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 to 300°C at a rate of 10°C/min under a

Table 1: Composition of Formulations

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

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 XRD profiles of LUMF, PIP, LUMF-PIP physical mixture, KOL, 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, KOL, 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 spectral range of 4000–500 cm^{-1} 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 of time samples (1-mL) were withdrawn, filtered through 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).

Statistical Analysis

Data obtained were expressed as mean ± SD and was analyzed by One way ANOVA. $p < 0.05$ was considered to determine the statistical significance.

Results and Discussion

Formulation and Solubility

Although concurrent dosing of PIP (a P-gp inhibitor) can enhance the poor and inconsistent bioavailability of LUMF, PIP has a modest bioavailability and solubility. Drug formulation as an SD employing the appropriate polymer/s can increase the solubility and bioavailability of the drug as well as the bioenhancer. Also, Jain *et al.* (2017) have reported the enhanced pharmacokinetics and bioavailability of LUMF from SD.[33] PIP is a recommended bioenhancer that is used at a rate of approximately 10% w/w of the drug in the formulation.[34] However, the solubility and bioavailability of PIP was improved from SD prepared with KOL as a polymer in the ratio 1:4 to 1:16.[35] Additionally, KOL was found to enhance the solubility and dissolution rate of LUMF from SD in the ratio 1:1 to 1:3 (LUMF:KOL).[36] LUMF has good glass forming ability and hence can be a good candidate for the synthesis of amorphous SD stable against crystallization prepared with fusion method.[19] Therefore, in the present study the ratios of 1:6:6, 1:6:12 and 1:6:18 (PIP:LUMF:KOL) were chosen to prepare LUMF-SD by employing melt method.

By achieving supersaturation, SD enhances the solubility of a dispersed drug (Lim *et al.*, 2015). The concentration of drug in the solution exceeds its solubility under supersaturation conditions, which leads to availability of greater amount of free drug in the solution for absorption. Saturation solubility studies exhibited the maximum solubility (69.36 ± 6.13 µg/mL) of pure LUMF in phosphate buffer pH 6.8. However, the SDs prepared with increasing ratio of polymeric carrier exhibited increased LUMF solubility SD in aqueous, 0.1 N HCl (pH 1.2) as well as phosphate buffer (pH 6.8) medium after 24 hours. Highest solubility of KOL containing LUMF-SD (1:6:18) was demonstrated in distilled water (316.01 ± 25.94 µg/mL) (Fig. 1A) followed by 163.71 ± 37.49 µg/mL (Fig. 1B) in acidic medium (0.1 N HCl pH 1.2) and 121.21 ± 26.91 µg/mL (Fig. 1C) in phosphate buffer (pH 6.8). The aqueous saturation solubility for pure LUMF after 24 hours was 42.14 ± 10.81 µg/mL which increased in LUMF-SD (1:6:18) with KOL by 649% (316.01 ± 25.94 µg/mL) (Fig. 1A), indicating enhanced LUMF aqueous solubility by KOL.

Dissolution Studies

Fig. 2 depicts the dissolution profiles of LUMF, and SD samples at various time points in distilled water, 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) under non-sink conditions. The pure drug, LUMF dissolved the slowest with the lowest final concentration of 38.36 ± 12.91 µg/mL in distilled water. A rapid and higher drug release at 8 h in distilled water was demonstrated by LUMF-SD prepared using KOL at ratio 1:6:18 (Fig. 1A) with a final concentration of 316.22 ± 22.51 µg/mL. The KOL containing LUMF-SD (1:6:18) released 118.27 ± 28.40 (Fig. 1B) and 153.15 ± 53.50 µg/mL (Fig. 1C) of LUMF in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8), respectively after 8 hours. The rate as well as extent of dissolution in all the three media found to be increased with increasing concentration of polymer in the SD. The amorphous state offers higher surface free energy than the crystalline form,

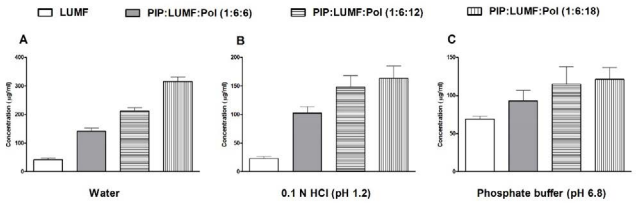

Fig. 1: Saturation solubility of LUMF alone and LUMF SD prepared with different ratios of KOL, in (A) water, (B) 0.1 N HCL (pH 1.2) and (C) phosphate buffer (pH 6.8).

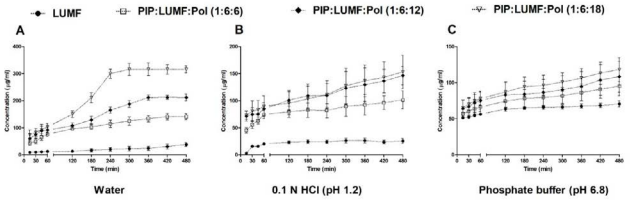

Fig. 2: Dissolution profiles of LUMF alone and LUMF SD prepared with different ratios of KOL, in (A) water, (B) 0.1 N HCL (pH 1.2) and (C) phosphate buffer (pH 6.8).

leading to higher solubility of a drug in amorphous form.[37] The drug in the SD system does not have to overcome the barrier of lattice energy for dissolving, in contrast to crystalline form, as amorphous SD include short-range intermolecular interactions.[38] Therefore, improved saturation solubility and dissolution of LUMF in SD can be attributed to its amorphous state attained in SD.

Irrespective of the medium, LUMF saturation solubility and dissolution was maximum from the SD containing the highest amount of polymeric carrier, signifying the enhancement of solubility and improved drug dissolution behavior with increased polymer content. The PIP-LUMF-KOL SD with the ratio of 1:6:18 showed maximum solubility and drug release in an aqueous medium and may contribute to the bioavailability enhancement of LUMF and hence was considered and characterized further.

DSC

The DSC thermographs of LUMF, PIP, KOL, physical mixture of LUMF: PIP, physical mixture of LUMF-PIP-KOL and PIP: LUMF: KOL (1:6:18) SD are shown in Fig. 3. The crystalline character of LUMF (Fig. 3A), PIP (Fig. 3B) and KOL (Fig. 3C) was demonstrated by the sharp endothermic peaks at 141.9 and 133.5°C, respectively, with enthalpies of 144.4 and 48.8 J/g, respectively. DSC thermogram of physical mixture of PIP- LUMF (1:6) displayed extended eutectic endothermic event of less energy (9.7 J/g) at 108.2°C earlier to that of LUMF or PIP (Fig. 3D). The DSC thermogram of physical mixture with KOL (Fig. 3E) was found to be devoid of melting endotherm for LUMF and PIP indicating the possible dissolution of drugs (LUMF and PIP) in the hot molten polymer through heating. The thermogram of PIP:LUMF:KOL SD revealed the shift of T_g of polymer to lower temperature, appearing as a mild and wide endothermic event devoid of any melting endotherm corresponding to either drugs, suggesting the amorphization of drugs during melting (Fig. 3F). Single depressed T_g observed during second DSC run of PIP-LUMF-KOL physical mixture (Fig. 3F) and SD (Fig. 3H) corroborate the formation of single phase of drugs with polymer during first run[39] and indicate the stability of amorphous drug in SD.

XRD

XRD was performed to determine the change in crystallinity. As depicted in Fig. 4A, 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° indicated the crystalline nature of LUMF (Fig. 4A). The characteristic crystalline intense peaks of PIP were observed at 2θ of 14.67, 19.55, 22.55, 25.78 and 28.19° (Fig. 4B). The decreased intensity of diffraction peaks displayed in diffractogram of physical mixture of LUMF and PIP suggests the partial loss of

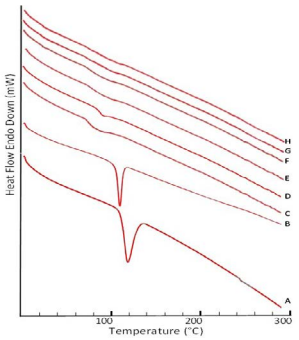

Fig. 3: DSC thermographs of A) LUMF, B) PIP, C) KOL, D) physical mixture of LUMF:PIP, E) physical mixture of LUMF:PIP:KOL, F) physical mixture of LUMF:PIP:KOL (Second Cycle), G) PIP:LUMF:KOL SD, H) PIP:LUMF:KOL SD (Second Cycle).

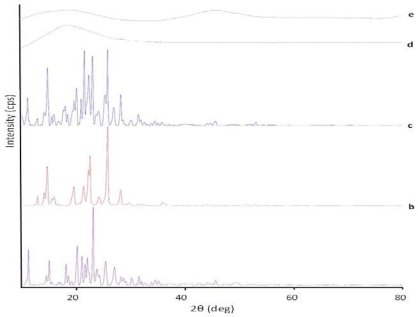

Fig. 4: XRD diffractogram of a) LUMF, b) PIP, c) physical mixture of LUMF:PIP, d) KOL and e) PIP: LUMF: KOL SD.

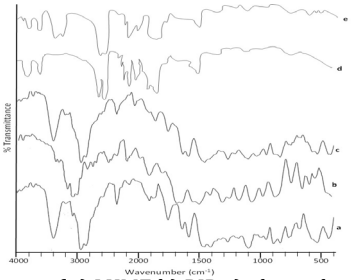

Fig. 5: FTIR spectra of a) LUMF, b) PIP, c) physical mixture of LUMF-PIP, d) KOL, e) PIP-LUMF-KOL SD.

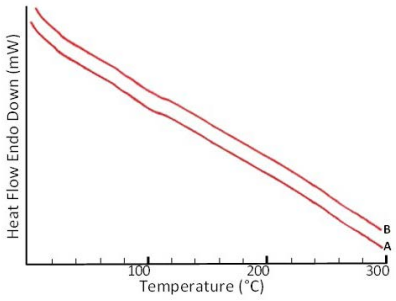

Fig. 6: DSC thermographs of LUMF- SD on day 0 (A) and day 90 (B). (LUMF-SD stored at stressed condition of 40 °C /75% RH.

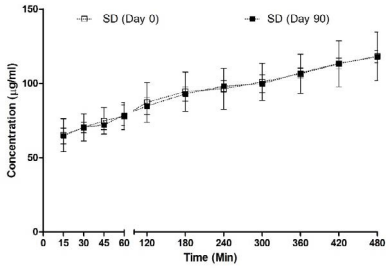

Fig. 7: Dissolution profiles of LUMF-SD on day 0 and day 90 (LUMF-Sd stored at stressed conditions of 40°C/75% RH).

crystallinity of drugs (Fig. 4C). Moreover, the absence of characteristic crystalline peak intensities of LUMF and PIP suggests amorphous state of drugs in SD (Fig. 4E). The increased aqueous solubility of LUMF in SD can be ascribed to the amorphous nature of PIP:LUMF:KOL in SD, confirmed by the XRD studies.

FTIR

FTIR analysis was performed to investigate possible interactions between the drugs and polymer in physical mixture and SD. Fig. 5 represents the spectra of LUMF, PIP, physical mixture of LUMF and PIP, KOL, and PIP: LUMF: KOL (1:6:18) SD. As depicted in Fig. 5A, LUMF has 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). The FTIR spectrum of PIP showed presence of 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) (Fig. 5B). The FTIR spectra of physical mixture of drugs found to be devoid of significant shift in characteristic peaks, indicating absence of chemical interaction between LUMF and PIP (Fig. 5C). Furthermore, the FTIR spectrum of SD showed the presence of drugs with their unchanged functional properties, indicating absence of chemical interactions between PIP and/or LUMF and KOL (Fig. 5E). As depicted in Fig. 5D, the peaks at 1740 and 1678 cm^{-1} are corresponded to the vinyl acetate and vinylpyrrolidone groups in KOL, respectively. The sharp peak at 1678 cm^{-1} broadened and shifted to 1682 cm^{-1} in SD spectrum, indicate the hydrogen bonding between LUMF and KOL.[40] The shift in carbonyl band of PIP from 1627 to 1639 cm^{-1} in SD represents the hydrogen bonding between PIP and KOL.[19] Thus, shifting of characteristic peaks of LUMF, PIP and KOL observed due to hydrogen bonding between LUMF, PIP and KOL. The hydrogen bonds between components of SD prevent the recrystallization of LUMF and PIP and facilitate the solubilization of LUMF.[15,41]

Stability

An amorphous, metastable state of drug in SD system is liable to recrystallization of drug to stable state and thus may affect the solubility and dissolution behavior. As depicted in Fig. 6, no significant difference in DSC thermograms of LUMF:PIP: KOL SD (1:6:18) 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 90 days storage under stress conditions (Fig. 7). The physical stability of SD can be ascribed to molecular interactions between drug and polymer, as observed in FTIR studies, leading to inhibition of molecular mobility and phase transition.

Conclusion

The aqueous solubility, extent, and rate of dissolution of LUMF from SD containing KOL was found to be improved. The molecular interactions between drugs and polymer were thought to preserve the amorphous state of LUMF in SD after storage under stressed conditions. Altogether, the study suggest that SD co-loaded with P-gp inhibitor can be employed as a feasible formulation strategy to improve aqueous solubility and thereby could improve the bioavailability of LUMF, contributing to the effective delivery of the drug and maximize its therapeutic benefits along with dose and/frequency reduction.

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References

1. Du Plessis LH, Govender K, Denti P, Wiesner L. In vivo efficacy and bioavailability of lumefantrine : Evaluating the application of Pheroid technology. Eur J Pharm Biopharm. 2015; 97:68-77.
2. Patel K, Sarma V, Vavia P. Design and evaluation of lumefantrine–oleic acid self-nanoemulsifying ionic complex for enhanced dissolution. DARU J Pharm Sci. 2013; 21(1):1-11.
3. White NJ, vanVugt M, Ezzet FD. Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. Clin Pharmacokinet. 1999; 37(2):105-125.
4. Wahajuddin M, Raju KS, Singh SP, Taneja I. Investigation of the functional role of P-glycoprotein in limiting the oral bioavailability of lumefantrine. Antimicrob Agents Chemother. 2014; 58(1):489-494.
5. Gahoi S, Jain GK, Tripathi R, Pandey SK, Anwar M, Warsi MH,

Singhal M, Khar RK, Ahmad, FJ. Enhanced antimalarial activity of lumefantrine nanopowder prepared by wet-milling DYNO MILL technique. Colloids Surf B Biointerfaces. 2012; 95:16-22.
6. Garg A, Bhalala K, Tomar DS. In-situ single pass intestinal permeability and pharmacokinetic study of developed lumefantrine loaded solid lipid nanoparticles. Int J Pharm. 2017; 516(1-2):120-130.
7. Bhatnagar P, Dhote V, Mahajan S, Mishra P, Mishra D. Solid dispersion in pharmaceutical drug development: from basics to clinical applications. Curr Drug Deliv. 2014; 11(2):155-171.
8. Baghel S, Cathcart H, O'Reilly NJ. Polymeric Amorphous Solid Dispersions: A Review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. J Pharm Sci. 2016;105(9):2527–2544.
9. Huang S, Mao C, Williams III RO, Yang CY. Solubility advantage (and disadvantage) of pharmaceutical amorphous solid dispersions. J Pharm Sci. 2016; 105(12):3549-3561.
10. Sathigari SK, Radhakrishnan VK, Davis VA, Parsons DL, Babu RJ. Amorphous-state characterization of efavirenz—polymer hot-melt extrusion systems for dissolution enhancement. J Pharm Sci. 2012; 101(9):3456–3464.
11. Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW. Amorphous Solid Dispersions: Theory and Practice. Springer, 2014.
12. Chiou, WL, Riegelman, S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971; 60(9):1281-1302.
13. Serajddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999; 88(10):1058-1066.
14. Teja SB, Patil SP, Shete G, Patel S, Bansal AK. Drug-excipient behavior in polymeric amorphous solid dispersions. J Excip Food Chem. 2013; 4(3):70–94.
15. Li Y, Pang H, Guo Z, Lin L, Dong Y, Li, G, Lu M, Wu, C. Interactions between drugs and polymers influencing hot melt extrusion. J Pharm Pharmacol. 2014; 66(2):148-166.
16. Aso Y, Yoshioka S. Molecular mobility of nifedipine -PVP and phenobarbital-PVP solid dispersions as measured by 13C-NMR spin-lattice relaxation time. J Pharm Sci. 2006; 95(2):318-325.
17. Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. Eur J Pharm Biopharm. 2008; 70(2) :493-499.
18. Bhardwaj V, Trasi NS, Zemlyanov DY, Taylor LS. Surface area normalized dissolution to study differences in itraconazole-copovidone solid dispersions prepared by spray-drying and hot melt extrusion. Int J Pharm. 2018; 540(1-2):106-119.
19. Trasi NS, Bhujbal SV, Zemlyanov DY, Zhou QT, Taylor LS. Physical stability and release properties of lumefantrine amorphous solid dispersion granules prepared by a simple solvent evaporation approach. Int J Pharm. 2020; 2:100052.
20. Bhujbal SV, Pathak V, Zemlyanov DY, Taylor LS, Zhou QT. Physical stability and dissolution of lumefantrine amorphous solid dispersions produced by spray anti-solvent precipitation. J Pharm Sci. 2021: 110(6):2423-2431.
21. Valkama E, Haluska O, Lehto VP, Korhonen O, Pajula K. Production and stability of amorphous solid dispersions produced by a Freeze-drying method from DMSO. Int J Pharm. 2021; 606:120902.
22. Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013; 85(3):799-813.
23. Mehanna MM, Motawaa AM, Samaha MW. In sight into tadalafil–block copolymer binary solid dispersion: mechanistic investigation of dissolution enhancement. Int J Pharm. 2010; 402(1-2):78-88.
24. Di L, Fish PV, Mano T. Bridging solubility between drug discovery and development. Drug Discov Today. 2012; 17(9-10):486-495.
25. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. Int Sch Res Notices. 2012; 3:1-10.
26. Varma MV, Panchagnula R. Enhanced oral paclitaxel absorption with vitamin E-TPGS: effect on solubility and permeability in vitro, in situ and in vivo. Eur J Pharm Sci. 2005; 25(4-5):445-453.
27. Ayrton A, Morgan P. Role of transport proteins in drug absorption, distribution and excretion. Xenobiotica. 2001; 31:469–497.
28. Kaur V, Garg T, Rath G, Goyal AK. Therapeutic potential of nanocarrier for overcoming to P-glycoprotein. J Drug Target. 2014; 22(10):859-870.
29. Athukuri BL, Neerati P, 2017 Enhanced oral bioavailability of domperidone with piperine in male wistar rats: involvement of CYP3A1 and P-gp inhibition. J Pharm Pharm Sci. 2017; 20:28-37.
30. Han Y, Tan TMC, Lim LY. In vitro and in vivo evaluation of the effects of piperine on P-gp function and expression. Toxicol Appl Pharmacol. 2008; 230(3):283-289.
31. Singh DV, Godbole MM, Misra K. A plausible explanation for enhanced bioavailability of P-gp substrates in presence of piperine: simulation for next generation of P-gp inhibitors. J Mol Model. 2013; 19(1):227-238.
32. Zhou S, Lim LY, Chowbay B. Herbal modulation of P-glycoprotein. Drug Metab Rev. 2004; 36(1): 57-104.
33. Jain JP, Leong FJ, Chen L, Kalluri S, Koradia V, Stein DS, Wolf MC, Sunkara G, Kota J. Bioavailability of lumefantrine is significantly enhanced with a novel formulation approach, an outcome from a randomized, open-label pharmacokinetic study in healthy volunteers. Antimicrob Agents Chemother. 2017; 61(9):e00868-17.
34. Majeed M, Badmaev V, Rajendran R. Use of piperine as a bioavailability enhancer. 1998. United States Patent Number, US005744161A.
35. Wdowiak K, Miklaszewski A, Pietrzak R, Cielecka-Piontek J. Amorphous system of hesperetin and piperine—improvement of apparent solubility, permeability, and biological Activities. Int J Mol Sci. 2023; 24(5):48-59.
36. Fule R, Meer T, Sav A, Amin, P. Solubility and dissolution rate enhancement of lumefantrine using hot melt extrusion technology with physicochemical characterization. J Pharma Invest. 2013; 43:305-321.
37. Grohganz H, Priemel PA, Löbmann K, Nielsen LH, Laitinen R, Mullertz A, Van den Mooter G, Rades, T. Refining stability and dissolution rate of amorphous drug formulations. Expert Opin Drug Deliv. 2014; 11(6):977-989.
38. Fule R, Dhamecha D, Maniruzzaman M, Khale A, Amin P. Development of hot melt co-formulated antimalarial solid dispersion system in fixed dose form (ARLUMELT): evaluating amorphous state and in vivo performance. Int J Pharm. 2015; 496(1):137-156.
39. Chokshi RJ, Zia H, Sandhu HK, Shah NH, Malick, WA. Improving the dissolution rate of poorly water-soluble drug by solid dispersion and solid solution—pros and cons. Drug Deliv. 2007; 14(1):33-45.
40. Liu J, Cao F, Zhang C, Ping Q. Use of polymer combinations in the preparation of solid dispersions of a thermally unstable drug by hot-melt extrusion. Acta Pharmaceutica Sinica B. 2013; 3(4):263-272.
41. Ashour EA, Majumdar S, Alsheteli A, Alshehri S, Alsulays B, Feng X, Gryczke A, Kolter K, Langley N, Repka, MA. Hot melt extrusion as an approach to improve solubility, permeability and oral absorption of a psychoactive natural product, piperine. J Pharm Pharm. 2016; 68(8):989-998.

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