RESEARCH ARTICLE

A Comparative Study of Influence of Different Polymers on Lumefantrine: Piperine Solid Dispersion

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ABSTRACT

To improve the oral delivery of biopharmaceutical classification system (BCS) class II drugs, solid dispersions techniques are generally adopted in drug product develoomment in pharmaceuticals. The choice of polymer in these designs significantly affects a drug's solubility and dissolution properties. The crystalline nature and the involvement of P-glycoprotein in active ingredient efflux further hinder drug absorption and bioavailability. In this study, solid dispersion (SD) of an antimalarial drug (lumefantrine) combined with piperine (a P-gp and CYP3A4 inhibitor), was created using different polymeric carriers: Soluplus, Klucel, Poloxamer, Povidone/PVP K30 (PVP), and Copovidone/Kollidon® VA64 (KOL). Among these, LUMF-PIP solid dispersion with SOL exhibited the maximum water solvency and fastest release across various media. These findings indicate that the choice of polymeric carrier significantly impacts LUMF's solubility and dissolution behavior in solid dispersion. SOL emerges as the most promising polymer for enhancing LUMF's solubility and dissolution, ultimately leading to improved bioavailability upon oral administration.

Keywords: Lumefantrine, Piperine, Polymers, Solid Dispersion, Solubility, Release.

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INTRODUCTION

Solid dispersion formulations have surfaced as a favorable approach for tackling the difficulties connected to poorly water-soluble molecules. In the pursuit of optimizing solid dispersion (SD) formulations, the choice of polymer plays a pivotal role. A significant determinant influencing the success of SD formulations is the choice of polymer. The selection of an appropriate polymer can significantly impact drug solubility, dissolution kinetics, stability, and overall therapeutic efficacy. In this chapter, a comparative study was done with different polymers. Effect on solubilization potential of the SD formulations studied which emphasizes the significance of polymer selection in drug formulation. Different polymers exhibit distinct physicochemical properties, like solubility, MW, and functional groups, that can significantly influence the behavior of solid dispersions. Diverse polymers influence the physical and chemical characteristics and effectiveness of SD systems.[1] By delving into this comparative analysis, we aim to elucidate the key factors governing the success of solid dispersion formulations in pharmaceutical development. Utilizing a drug in its amorphous form could serve as a beneficial method for enhancing the dissolution characteristics and bioaccessibility of inadequately aqueous soluble drugs.[2,3] However, amorphous substances exhibit thermodynamic instability and can potentially undergo recrystallization over time because of their high free energy. Consequently, pharmaceutical scientists have explored various approaches to advance the bioavailability of inadequately aqueous solvable API. Among these strategies, SD developed as a versatile and promising method.[4]

SD is a technique in which molecules are dispersed in a polymeric carrier. This process results in improved drug solubility and dissolution rates, potentially revolutionizing the delivery of inadequately aqueous soluble drugs.[5] SD formulations have the potential to mitigate the need for high drug doses, decrease adverse effects, and enhance compliance to patients by offering faster and more reliable drug absorption.[6] The physical and chemical characteristics of API and excipients influence the properties of resultant solid dispersion.[7] Concentration of drug achieved through solid dispersion during dissolution significantly surpasses that obtained with the kinetically steady crystalline drug property, demonstrating the creation of a super-saturated solution. Additionally, the interaction of the drug with the polymer in the solution results in an enhanced equipoise solubility are the governing factor that enhances solution concentration following the dissolution of solid dispersions.[8]

LUMF a crystalline antimalarial compound falling within biopharmaceutical classification system (BCS) II, exhibits limited solubility in aqueous solutions and displays inconsistent

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oral bioavailability, as discussed.[9] The poor solvency in water, active efflux mediated by P-glycoprotein and deactivation by CYP3A4 collectively affect to the challenges in achieving high bioavailability of the drug, as observed.[10] The current study's objective is to evaluate and compare the effectiveness of five different polymers, namely Soluplus, Klucel EF, Poloxamer, PVP K30, and Kollidon VA64, in enhancing the solubilization and drug release of LUMF. This enhancement is achieved through the formulation of SD along with PIP.

MATERIAL AND METHODS

Reagents and Ingredients

Poloxamer 188 (Lutrol), Cipla, Mumbai, soluplus (Cipla, Mumbai), hydroxypropyl cellulose (Klucel) (Cipla, Mumbai), Povidone (KVP K30) (Cipla, Mumbai), copovidone (Kollidon® VA64) (Cipla, Mumbai) and lumefantrine (Cipla Ltd, Mumbai).

Procedures for Solid Dispersion

SD was created through the melting technique. Briefly, suitable amounts (refer to Table 1) of lumefantrine and piperine were introduced into earlier molten polymers (SOL, KLU, LUT, PVP, and KOL) in a ceramic dish placed on a hot plate, with constant mixing to achieve a uniform dispersion. The melting procedure was conducted at temperatures of 60°C for LUT, 75°C for SOL, 110°C for KOL, 130°C for KLU and PVP. The resultant mixture was chilled using an ice bath and placed in a desiccating chamber for a duration of 24 hours. Following this, the mixture was subjected to grinding in a mortar and sifted using a 30-size sieve. The amorphous nature of drugs in SD was established by the absence of endothermic peaks of drugs in the obtained thermographs, as revealed by differential scanning calorimetry (DSC).[11,12]

The proportion of piperine was kept constant at 0.167 parts compared to the drug.

Solubility Assessments

The saturation solubility of lumefantrine solid dispersion was evaluated using water, acidic media (0.1 N HCl), and basic media (buffer pH 6.8). In brief, 100 mg of drug and solid dispersion were introduced into separate containers with 100 mL of each media. The mixture underwent stirring for 24 hours at RT. Samples were withdrawn after 24 hours and analyzed by HPLC to determine lumefantrine concentration. [11-12]

Dissolution Assessments

The dissolution study of pure LUMF and solid dispersions 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 solid dispersion 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 of time, filtered through a nylon syringe filter (0.45 µm; J-Sil Scientific Industries, Agra, India), and were subjected to LUMF analysis using HPLC. The HPLC system equipped with Jasco PU2080 plus pumps with PDA detector and autosampler unit was employed. The LUMF released was quantified using the HPLC method reported earlier. [11,12]

RESULTS AND DISCUSSION

Solubility Assessments

Pure LUMF exhibited the highest (69.36 ± 6.14 µg/mL) solubility in basic buffer (Phosphate - pH 6.8). In 0.1 N HCl acidic medium (pH 1.2) LUMF solid dispersion prepared with SOL showed maximum (284.63 ± 34.87 µg/mL) solubility in acidic medium (pH 1.2). Subsequently LUT (276.63 ± 35.72 µg/mL), KOL (163.71 ± 37.49 µg/mL), KLU (130.35 ± 48.17 µg/mL) and PVP (108.27 ± 41.49 µg/mL) (Figure 1B). On the other hand, basic buffer (Phosphate - pH 6.8) LUMF solubility from solid dispersion prepared with LUT was highest (274.88 ± 57.29 µg/mL) followed by SOL (272.98 ± 57.29 µg/mL), KLU (143.99 ± 22.92 µg/mL), KOL (121.19 ± 27.00 µg/mL) and PVP (119.10 ± 23.12 µg/mL) (Figure 1C).

After 24 hours pure LUMF showed aqueous solubility of 42.14 ± 10.85 µg/mL. However, it was found to be increased from solid dispersion prepared with SOL (330.57 ± 35.18 µg/mL) followed by KOL (311.01 ± 17.49 µg/mL), KLU (158.69 ± 11.73 µg/mL), PVP (121.01 ± 13.99 µg/mL) and LUT (103.18 ± 6.40 µg/mL) (Figure 1A). Overall, the solubility studies demonstrated the polymer-dependent solubility of LUMF from the solid dispersion. The enhancement in the aqueous solubility of LUMF from solid dispersions prepared with different polymers was found to be in the order of SOL>KOL> KLU > PVP > LUT (Tables 2-4).

Solid dispersion improves the dissolvability of the distributed API by attaining supersaturation and the polymers can stabilize the supersaturated solution (Konno *et al*., 2008).

Table 1: Formulations composition

Compositions	*Lumefantrine-Polymer proportion*	
	Lumefantrine	*Polymer*
LUMF:SOL	1	3
LUMF:KLU	1	3
LUMF:LUT	1	3
LUMF:PVP	1	3
LUMF:PVP	1	3

Table 2: Solubility of pure lumefantrine and lumefantrine solid dispersion formulated using SOL, KLU, LUT, PVP and KOL in water (aqueous medium)

Formulation code	*Solubility (µg/mL)*	
	Mean	*SD*
LUMF	42.14	10.85
LUMF:PIP:SOL	330.57	35.18
LUMF:PIP:KLU	158.69	11.73
LUMF:PIP:LUT	103.18	6.40
LUMF:PIP:KOL	311.01	17.49
LUMF:PIP:PVP	121.01	13.99

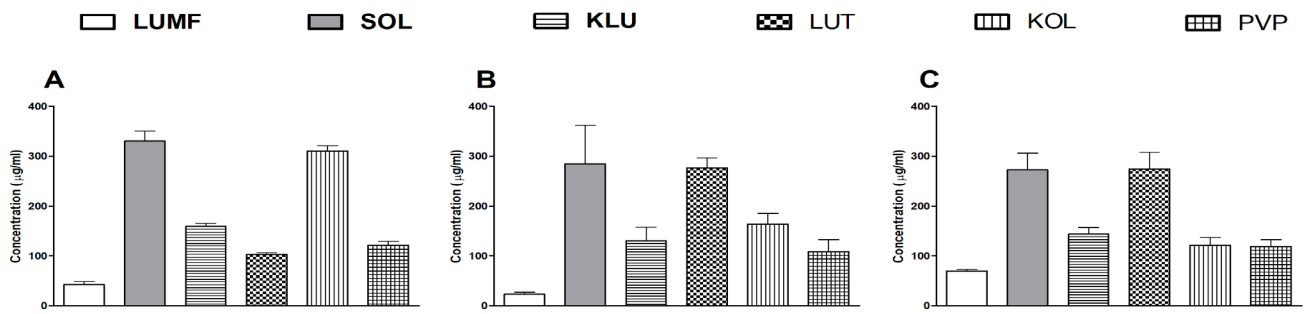

Figure 1: Pure lumefantrine and lumefantrine solid dispersion were prepared with different polymers solubility data in A) aqueous, B) acidic and C) basic medium

Table 3: Data for lumefantrine and lumefantrine solid dispersion formulated using SOL, KLU, LUT, PVP and KOL in 0.1 N HCL (pH 1.2)

Formulation code	*Solubility (µg/mL)*	
	Mean	*SD*
LUMF	23.08	6.56
LUMF:PIP:SOL	284.63	34.87
LUMF:PIP:KLU	130.35	48.17
LUMF:PIP:LUT	276.63	35.72
LUMF:PIP:KOL	163.71	37.49
LUMF:PIP:PVP	108.27	41.49

Table 4: Data for solubility of pure lumefantrine and lumefantrine solid dispersion formulated using SOL, KLU, LUT, PVP and KOL with basic medium

Formulation code	*Solubility (µg/mL)*	
	Mean	*SD*
LUMF	69.36	6.14
LUMF:PIP:SOL	272.98	57.29
LUMF:PIP:KLU	143.99	22.92
LUMF:PIP:LUT	274.88	57.29
LUMF:PIP:KOL	121.19	27.00
LUMF:PIP:PVP	119.10	23.12

Dissolution Assessments

Pure lumefantrine dissolved slowly and attained the minimal concluding concentration value 37.79 ± 13.10 µg/mL in an aqueous medium (Table 5, Figure 2A). However, solid dispersion composed of SOL demonstrated a higher rate and extent of dissolution of the drug at the eight-hour interval with a final concentration of 333.01 ± 33.67 µg/mL, followed by KOL (316.22 ± 11.73 µg/mL), KLU (138.67 ± 11.73 µg/mL), PVP (121 ± 11.73 µg/mL) and LUT (95.54 ± 11.73 µg/mL). Furthermore, SOL containing solid dispersion displayed improved dissolution in the acidic medium and basic medium in comparison with solid dispersions containing other polymers under investigation (Figure 2B). The SOL containing solid dispersion released 178.54 ± 35.19 µg/mL and 129.08 ± 44.27 µg/mL of lumefantrine in the acidic medium and basic medium, correspondingly. The solid dispersion prepared with PVP demonstrated the lowest rate and extent of LUMF dissolution in an acidic medium (Table 6, Figure 2B) as well as basic medium (Table 7, Figure 2C). Whereas, in distilled water, LUT-composed solid dispersion released the LUMF at the minimal concluding concentration value 95.54 ± 5.73 µg/mL (Table 5).

In the drug's crystalline form, the lattice structure needs to be disturbed for the substance to undergo dissolution. While owing to brief intermolecular interactions occurring in an amorphous state, the drug is not required to surmount the lattice energy hindrance for dissolvability (Aisha *et al.*, 2012). Therefore, the rise in solubility and release rate and extent of lumefantrine in solid dispersion can be related to its non-crystalline form achieved for solid dispersion. Moreover, the drug's highest release values from solid dispersion prepared with SOL compared to all other polymers under study can be accredited to the hydrophilic characteristic of SOL. Hydrophilic carriers contribute to improving wettability

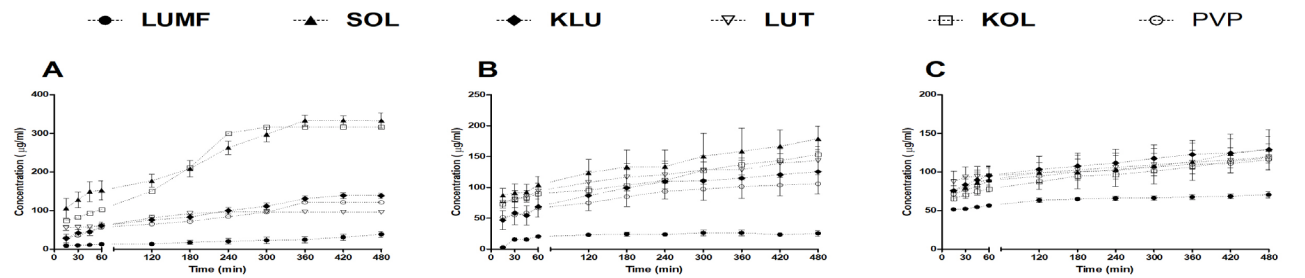

Figure 2: The release data of pure lumefantrine and lumefantrine solid dispersion formulated using different polymers in three mediums (A) aqueous, B) acidic and C) basic.

Table 5: The release data of pure lumefantrine and lumefantrine solid dispersion formulated using different polymers SOL, KLU, LUT, PVP, and KOL in distilled water

Time (Min)	*Formulation code*					
	Solubility (µg/mL) (Mean ± SD)					
	LUMF	*LUMF:SOL*	*LUMF:KLU*	*LUMF:LUT*	*LUMF:KOL*	*LUMF:PVP*
15	9.10 ± 3.47	105.78 ± 43.66	27.53 ± 20.74	54.96 ± 11.11	73.32 ± 31.96	29.17 ± 9.90
30	9.69 ± 3.84	127.69 ± 34.43	42.10 ± 14.86	56.45 ± 9.99	83.08 ± 24.83	35.17 ± 11.11
45	11.09 ± 4.65	148.89 ± 45.65	44.53 ± 16.68	57.61 ± 5.73	93.01 ± 35.35	44.54 ± 11.80
60	12.87 ± 6.19	152.25 ± 42.91	60.38 ± 15.92	60.58 ± 6.73	103.05 ± 21.50	56.73 ± 10.89
120	13.17 ± 6.38	177.10 ± 28.53	75.28 ± 12.36	80.54 ± 13.89	150.00 ± 21.13	64.45 ± 7.30
180	17.28 ± 9.84	208.50 ± 36.03	83.10 ± 13.31	92.24 ± 7.65	211.36 ± 32	71.50 ± 15.12
240	20.26 ± 11.69	262.50 ± 29.88	99.98 ± 15.16	96.59 ± 6.52	300.04 ± 28.49	84.00 ± 7.67
300	22.51 ± 15.22	296.93 ± 32.45	110.96 ± 15.04	96.44 ± 6.08	316.22 ± 39.07	95.71 ± 11.85
360	24.24 ± 14.26	333.15 ± 24.72	130.69 ± 12.21	96.29 ± 8.76	316.22 ± 40.07	121.05 ± 11.31
420	30.78 ± 15.19	333.88 ± 19.14	138.59 ± 13.36	95.67 ± 4.79	316.20 ± 30.75	121.00 ± 10.56
480	37.79 ± 13.10	333.01 ± 33.67	138.67 ± 11.59	95.54 ± 5.73	316.22 ± 22.51	121.00 ± 9.23

Table 6: The release data of pure lumefantrine and lumefantrine solid dispersion formulated using different polymers SOL, KLU, LUT, PVP, and KOL in 0.1 N HCL (pH 1.2)

Time (Min)	*Formulation code*					
	Solubility (µg/mL) (Mean ± SD)					
	LUMF	*LUMF:SOL*	*LUMF:KLU*	*LUMF:LUT*	*LUMF:KOL*	*LUMF:PVP*
15	2.81 ± 3.06	87.13 ± 19.75	46.88 ± 26.43	75.89 ± 15.59	72.96 ± 12.74	51.63 ± 19.64
30	15.76 ± 3.44	91.02 ± 25.37	58.39 ± 32.63	81.00 ± 23.91	80.46 ± 32.62	55.27 ± 25.66
45	15.83 ± 2.81	92.02 ± 22.80	54.54 ± 27.21	86.45 ± 15.88	83.41 ± 30.06	58.27 ± 27.90
60	20.31 ± 2.88	103.83 ± 23.72	69.01 ± 28.85	94.05 ± 22.19	89.87 ± 33.24	66.71 ± 21.72
120	23.10 ± 4.61	123.20 ± 38.32	86.63 ± 42.08	107.78 ± 31.07	95.53 ± 36.54	74.69 ± 39.59
180	24.28 ± 5.81	133.22 ± 47.01	98.90 ± 51.35	116.63 ± 38.77	103.42 ± 40.56	84.77 ± 40.50
240	23.87 ± 5.54	133.7 ± 46.49	109.67 ± 50.17	120.22 ± 38.49	111.26 ± 44.43	93.53 ± 41.66
300	26.39 ± 7.97	150.3 ± 64.44	110.67 ± 53.66	128.21 ± 39.79	127.38 ± 56.25	97.09 ± 39.28
360	26.29 ± 8.18	158.1 ± 65.59	114.95 ± 56.79	128.36 ± 27.76	136.91 ± 50.68	101.12 ± 38.93
420	23.50 ± 5.49	166.55 ± 45.01	120.32 ± 59.07	139.12 ± 40.42	143.23 ± 50.33	103.61 ± 40.89
480	25.44 ± 8.03	178.54 ± 35.19	125.28 ± 62.14	143.29 ± 39.34	153.15 ± 53.50	105.78 ± 42.56

Table 7: The release data of pure lumefantrine and lumefantrine solid dispersion formulated using different polymers SOL, KLU, LUT, PVP, and KOL in basic medium (phosphate -pH 6.8)

Time (Min)	*Formulation code*					
	Solubility (µg/mL) (Mean ± SD)					
	LUMF	*LUMF:SOL*	*LUMF:KLU*	*LUMF:LUT*	*LUMF:KOL*	*LUMF:PVP*
15	51.35 ± 2.55	76.39 ± 24.13	75.77 ± 11.52	87.15 ± 23.77	65.12 ± 19.22	71.31 ± 13.19
30	52.14 ± 2.65	79.65 ± 24.59	83.41 ± 12.48	93.44 ± 22.96	70.30 ± 15.92	76.59 ± 16.87
45	54.58 ± 3.28	86.96 ± 28.21	89.55 ± 17.57	94.20 ± 22.29	74.72 ± 15.62	81.22 ± 17.52
60	56.41 ± 2.86	89.70 ± 26.89	95.15 ± 21.22	94.76 ± 22.33	77.98 ± 15.77	88.77 ± 17.30
120	63.28 ± 4.86	99.09 ± 37.33	103.30 ± 29.04	98.82 ± 22.49	87.18 ± 23.27	94.26 ± 23.27
180	64.83 ± 3.62	99.81 ± 37.31	107.48+29.26	102.65 ± 24.22	94.45 ± 22.96	99.97 ± 23.06
240	65.83 ± 4.78	102.83 ± 37.63	111.54 ± 30.68	105.80 ± 26.17	96.34 ± 24.10	101.89 ± 23.06
300	66.29 ± 4.86	107.60 ± 39.53	117.32 ± 30.85	109.44 ± 25.36	100.94 ± 21.84	106.38 ± 21.06
360	67.47 ± 5.41	113.09 ± 42.49	122.60 ± 31.56	112.57 ± 26.26	106.47 ± 22.87	109.93 ± 24.62
420	68.39 ± 5.45	123.57 ± 43.91	124.25 ± 32.56	115.24 ± 28.09	113.23 ± 26.86	110.79 ± 25.34
480	70.50 ± 7.08	129.08 ± 44.27	128.78 ± 29.89	119.42 ± 29.48	118.28 ± 28.41	115.47 ± 25.55

and decreasing the surface tension between the dissolution medium and molecule (Carneiro *et al.*, 2019). Different polymers demonstrated variation in solubility and dissolution behavior of LUMF in solid dispersion. The SOL containing solid dispersion displayed comparatively the fastest and highest drug release in all the three dissolution media employed in the present study. These results suggest that SOL could be the best choice in the formulation for LUMF SD to enhance its solvency and dissolution behavior consequently leading to improved bioavailability of LUMF.

CONCLUSION

The current investigation was conducted to investigate the effect of various carriers, SOL, KLU, LUT, Povidone and KOL, assessing the solubility and release behavior of the LUMF SD formulated by employing the melting technique. The enhanced solvency and release of lumefantrine from different solid dispersions were found to be polymer-dependent. Among the polymers under investigation, SOL-composed solid dispersion displayed the highest solubility of LUMF in aqueous and acidic media. Moreover, it demonstrated the highest amount and degree of release in all three release media. Therefore, the results of the present study suggest that the selection of a type of polymer is a viable approach for enhancing the solubility and dissolution of drugs exhibiting poor aqueous solubility and eventually enhancing their bioavailability.

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