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(RESEARCH ARTICLE)

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Preparation and evaluation of solid dispersion of Lumefantrine for dissolution enhancement

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Abstract

The prime challenge of poorly soluble drug is its solubility and dissolution. In the present study class II drug Lumefantrine (LUM) was selected for enhancing the solubility and dissolution by solid dispersion (SDs) technique using hydrophilic polymers. Solid dispersions of LUM were prepared by physical mixture, solvent evaporation and kneading method using hydrophilic polymers viz., maltodextrin and HPC at 1:1 and 1:3 ratios. The SDs was characterized for drug content and in vitro dissolution studies. The drug excipient interactions were studied by FTIR. Further in vitro data was interpreted by using PCP Disso V3 software with possible model fitting. One way ANOVA was studied at 95% CI. Preformulation studies found to be satisfactory. FTIR studies showed no interaction between drug and added hydrophilic polymers. One Way ANOVA results indicated increased dissolution in case of SDs prepared by solvent evaporation and kneading method at both the ratios when compared to physical mixture and pure drug. The present study concludes that SD technique can be successfully applied to increase the solubility and dissolution of poorly soluble drug Lumefantrine using hydrophilic polymers.

Keywords: Lumefantrine; HPC; Maltodextrin; Anova; FTIR

1. Introduction

Solubility enhancement of poorly water-soluble drugs is a crucial issue to improve their solubility and bioavailability. In recent years, due to application of combinational chemistry and high throughput screening during drug discovery, a majority of new drug candidates exhibits poor aqueous solubility. Such compounds are very challenging for formulation scientists in developing bioavailable dosage forms. Poorly water-soluble compound has classically been defined as one dissolving in less than 1 part per 10000 part of water[1]. A poorly water-soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract[2]. Thus, a greater understanding of dissolution and absorption behaviours of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of poorly soluble compounds might be improved to minimize the limitations to oral bioavailability.

$$dC/dt=(AD(C_S-C_b))/hV$$

Where, dc/dt = Rate of dissolution

- A = Surface area available for dissolution
- D = Diffusion coefficient of the compound
- Cs = Solubility of the compound in the dissolution medium

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- Cb = Concentration of drug in the medium at time
- h = Thickness of the diffusion boundary layer adjacent to surface of the dissolving compounds
- V = Volume of dissolution media

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound to decrease the boundary layer thickness, to ensure sink conditions for dissolution and last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

Lumefantrine (LUM) is indicated for the treatment of malaria, used alone or in combination with other anti-malarial agents. LUM is insoluble in water but soluble in chloroform and in most organic solvents, slightly soluble in propanol, almost insoluble in ethanol. LUM drug belong to class II under BCS and exhibit low and variable oral bioavailability due to is poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability[3-7]. The purpose of the present study was to prepare the solid dispersions (SDs) by using various hydrophilic carriers and containing Lumefantrine with an intension to enhance the solubility and dissolution rate.

2. Material and Methods

2.1. Materials

The drug Lumefantrine (LUM) was obtained as a gift sample from AET Pharmaceuticals, Hyderabad. Maltodextrin (Malto) was procured from Hi Media Laboratories, Mumbai. HPC was procured from Yarrow Chem products. Dichloromethane (DCM) was procured from SD fine chemicals, Mumbai.

2.2. Methods

2.2.1. Preparation of physical mixtures (PMs) and SDs

LUM: Malto and LUM: HPC at 1:1 and 1:3 ratios were prepared by mixing individual components together with a spatula and kept in desiccators for further study. Similarly, SDs of LUM were prepared by kneading and solvent evaporation method with Malto and HPC at 1:1 and 1:3 ratios.

2.2.2. Solvent evaporation systems (SE)

SDs containing LUM: Malto and LUM: HPC at 1:1 and 1:3 ratios were prepared by SE method. The required amount of LUM was dissolved in DCM and excipient was dispersed in the drug solution. The solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #80 and stored in desiccators until further evaluation.

2.2.3. Kneaded systems (KNE)

SDs containing LUM: Malto and LUM: HPC at 1:1 and 1:3 ratios were prepared by KNE method. The drug and excipient were weighed accordingly to the specified drug: carrier ratio and was taken in a glass mortar. The mixture was triturated slowly with DCM for 1 hr take care that the damp mass was maintained throughout the trituration period. Further mass was dried under vacuum, pulverized and sieved through #80 and stored in desiccators for further study.

2.3. Evaluation of solid dispersion systems

2.3.1. Saturation solubility

The saturation solubility studies were carried out for pure drug, PMs and SDs. Weighed amount of LUM, PMs and all prepared SDs equivalent to 20 mg of LUM were dispersed in 25 ml vials containing 20 ml of 0.1 N HCl. The sealed vials were shaken on rotary shaker for 24 hr at room temperature and equilibrated for 48 hr. An aliquot was passed through 0.45 µ nylon disc filter and the filtrate was suitably diluted with 0.1 N HCl and measured the absorbance at 341 nm and estimate the LUM content using the calibration curve.

2.3.2. Drug content uniformity

In each case PMs and SDs powder equivalent to 20 mg of LUM was accurately weighed and transferred to 50 ml volumetric flask. To this methanol was added to dissolve the LUM. Filter if necessary and 1ml of this filtrate was taken

in a 100 ml volumetric flask and made up to 100 ml with 0.1N HCl and measure the absorbance at 341 nm and estimate the LUM content using the calibration curve.

2.3.3. Dissolution studies

In vitro dissolution studies of LUM, PMs and all SDs were carried out in 900 ml 0.1N HCl using a USPXXI type 2 dissolution test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 20 mg of LUM, speed of 50 rpm and a temperature of 37^0C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered using a 0.45 µm nylon disc filter and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for LUM content by measuring the absorbance at 341 nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0.

3. Results

3.1. Drug content studies

The percentage drug content for all the prepared PMs and its SDs were calculated with SD values. The obtained data were given in tables 1 and 2.

3.2. Saturation solubility studies

The saturation solubility of LUM from PMs and its SDs were carried out in 0.1N HCl. The solubility data were given in tables 3 and 4. The solubility of LUM was found to be 1.762 ± 0.0129 M $x10^{-3}$.

Table 1 LUM drug content in PMs and its SDs prepared with Malto

Code	Drug: polymer	Amount of drug taken	Amount of drug recovered Mean* ± SD	% Drug content Mean* ± SD
F1	1:1	20mg	18.00 ± 0.106	90.00 ± 0.534
F2	1:3	20mg	19.20 ± 0.111	96.00 ± 0.556
F3	1:1	20mg	18.96± 0.066	94.80 ± 0.332
F4	1:3	20mg	19.99 ± 0.101	99.50 ± 0.726
F5	1:1	20mg	19.40± 0.072	97.00 ± 0.361
F6	1:3	20mg	19.60 ± 0.040	98.00 ± 0.202

*Average of three determinations

Table 2 LUM content in PMs and its SDs prepared with HPC

Code	Drug: polymer	Amount of drug taken	Amount of drug recovered Mean* ± SD	%Drug content Mean* ± SD
F7	1:1	20mg	19.66±0.0057	98.30 ± 0.028
F8	1:3	20mg	19.73±0.0152	98.65± 0.076
F9	1:1	20mg	18.96±0.0208	94.80± 0.104
F10	1:3	20mg	19.16±0.0115	95.80± 0.057
F11	1:1	20mg	19.43±0.0152	97.15± 0.076
F12	1:3	20mg	19.76±0.0251	98.80± 0.125

*Average of three determinations

Table 3 Saturation solubility data of LUM in PMs and its SDs prepared with Maltodextrin

Code	Drug	Polymer	Ratio	Method	Concentration M×10^{-3} ± SD*
F1	LUM	Malto	1:1	PM	2.34 ± 0.0016
F2	LUM	Malto	1:3	PM	2.46 ± 0.0024
F3	LUM	Malto	1:1	SE	4.54 ± 0.0016
F4	LUM	Malto	1:3	SE	4.85 ± 0.0042
F5	LUM	Malto	1:1	KNE	5.03 ± 0.0038
F6	LUM	Malto	1:3	KNE	5.15 ± 0.0047

*Average of three determinations

Table 4 Saturation solubility data of LUM in PMs and its SDs prepared with HPC

Code	Drug	Polymer	Ratio	Method	Concentration M×10^{-3} ± SD*
F7	Lumefantrine	HPC	1:1	PM	2.51 ± 0.0053
F8	Lumefantrine	HPC	1:3	PM	2.62 ± 0.0017
F9	Lumefantrine	HPC	1:1	SE	4.73 ± 0.0047
F10	Lumefantrine	HPC	1:3	SE	4.84 ± 0.0015
F11	Lumefantrine	HPC	1:1	KNE	5.63 ± 0.0020
F12	Lumefantrine	HPC	1:3	KNE	5.74 ± 0.0056

*Average of three determinations

3.3. FTIR studies

The FTIR spectrum of LUM, and its SDs prepared by kneading methods at 1:3 was recorded and shown in figures 1 and 2.

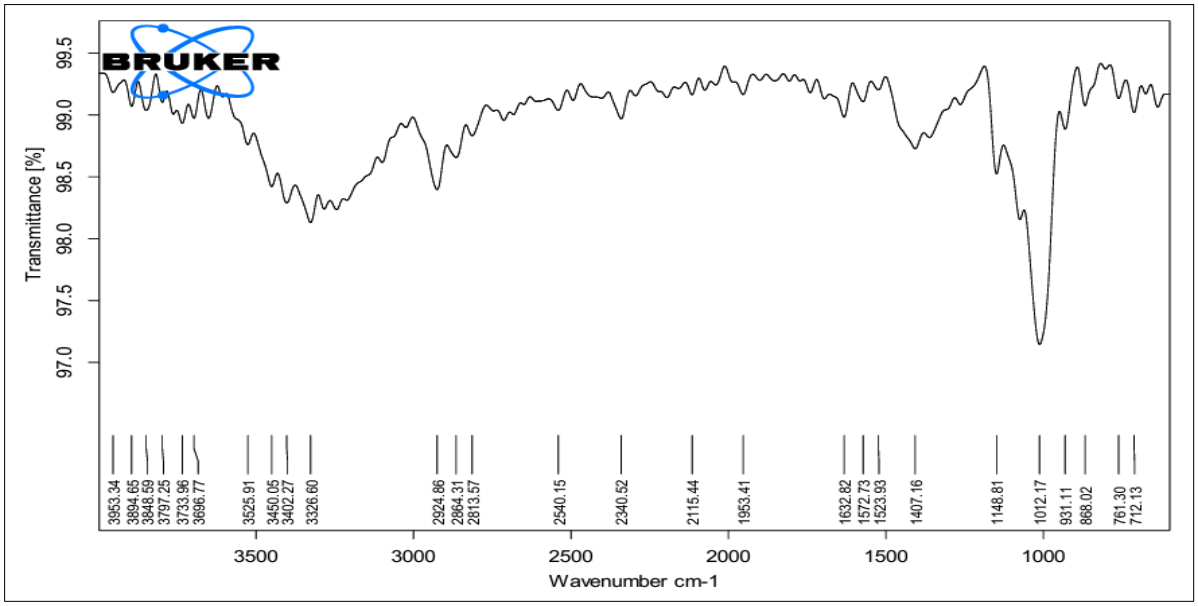

Figure 1 FTIR spectra of HF6 formulation (KN 1:3 ratio)

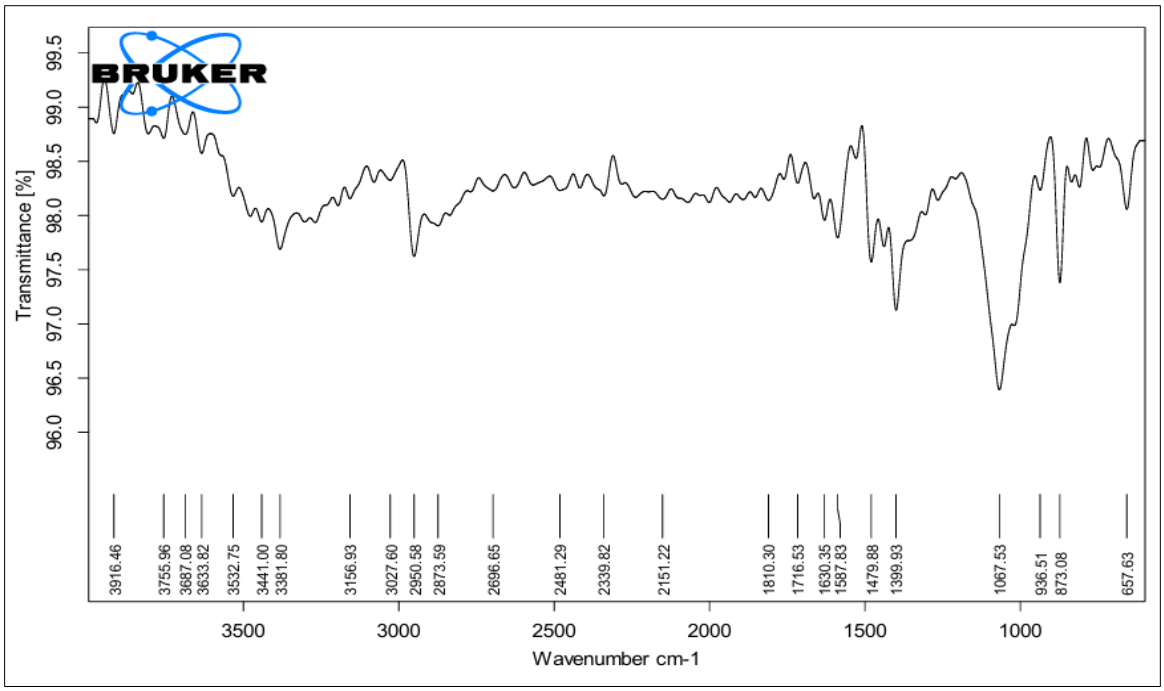

Figure 2 FTIR spectra of HF12 formulation (KN 1:3 ratio)

3.4. Dissolution studies

The dissolution data and profile were studied by using dissolution software PCP Disso V3.0. The dissolution data, profiles with model fitting data were presented in figures 3 and 4, tables 5 and 6.

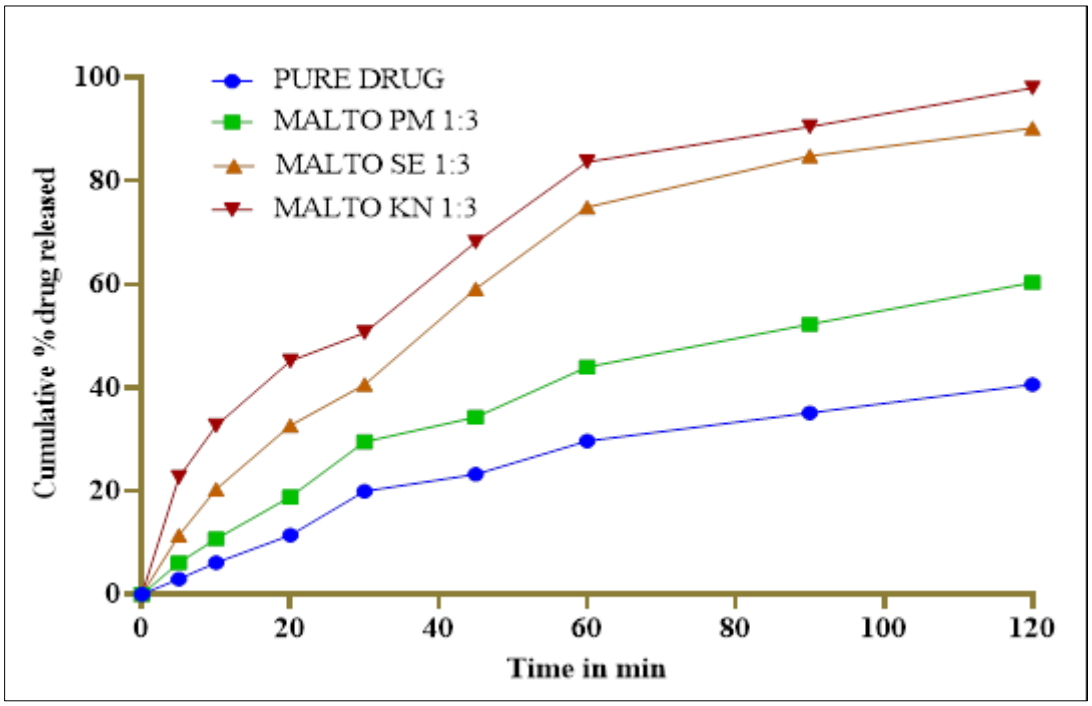

Figure 3 Comparative dissolution profiles of LUM and its SDs with Malto at 1:3 ratio

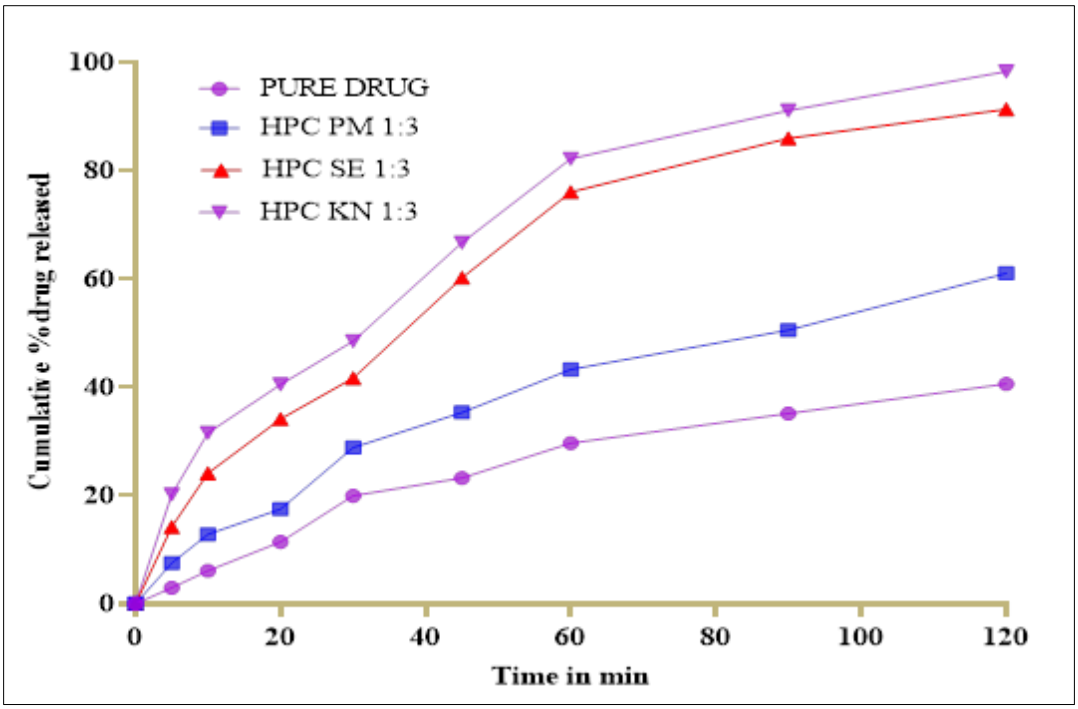

Figure 4 Comparative dissolution profiles of LUM and its SDs with HPC at 1:3 ratio

Table 5 Dissolution parameters and best model fitting curve data LUM, PMs and its SDs prepared with Malto at 1:1 and 1:3 ratios

Batches		**DE_{30} (%)**	**DE_{60} (%)**	**DP_{30}**	**DP_{60}**	**T_{50} (min)**	**RDR_{30}**	**RDR_{60}**	**MDT_{30}**	**First order rates $K1\times10^2$ (min^{-1})**		**Hix.crow $KHC\times10^2$ ($mg^{1/3}.min^{-1}$)**	
										R	K1	R	KHC
Pure drug		9.17	16.60	19.95	29.69	141.8	1	1	16.21	0.9677	-0.0049	0.9590	-0.0015
PM	1:1	13.66	21.71	24.60	36.50	106.5	1.48	1.30	13.35	0.9670	-0.0065	0.9530	-0.0020
PM	1:3	14.22	24,86	29.54	43.96	82.8	1.55	1.49	15.56	0.9831	-0.0084	0.9702	-0.0025
SE	1:1	21.50	34.21	37.73	58.59	50.5	2.34	2.06	12.91	0.9965	-0.0137	0.9845	-0.0037
SE	1:3	25.25	41.85	40.61	74.93	34.2	2.75	2.52	11.35	0.9950	-0.0203	0.9802	-0.0050
KNE	1:1	29.09	45.92	44.86	79.32	28.3	3.17	2.76	10.56	0.9970	-0.0245	0.9839	-0.0057
KNE	1:3	35.42	51.54	50.65	83.66	23.3	3.58	3.10	9.02	0.9871	-0.0298	0.9806	-0.0064

Table 6 Dissolution parameters and best model fitting curve data LUM, PMs and its SDs prepared with HPC at 1:1 and 1:3 ratios

Batches		**DE_{30} (%)**	**DE_{60} (%)**	**DP_{30}**	**DP_{60}**	**T_{50} (min)**	**RDR_{30}**	**RDR_{60}**	**MDT_{30}**	**First order rates $K1\times10^2$ (min^{-1})**		**Hix.crow $KHC\times10^2$ ($mg^{1/3}.min^{-1}$)**	
										R	K1	R	KHC
Pure drug		9.17	16.60	19.95	29.69	141.8	1	1	16.21	0.9677	-0.0049	0.9590	-0.0015
PM	1:1	13.84	23.30	27.06	39.70	98.7	1.50	1.40	14.66	0.9659	-0.0070	0.9512	-0.0021
PM	1:3	15.11	25.40	28.84	43.27	83.3	1.64	1.53	14.29	0.9829	-0.0083	0.9698	-0.0025
SE	1:1	22.86	35.43	38.81	59.68	48.8	2.49	2.13	12.33	0.9956	-0.0142	0.9820	-0.0038
SE	1:3	26.73	43.14	41.70	76.03	32.7	2.91	2.59	10.77	0.9955	-0.0212	0.9797	-0.0052
KNE	1:1	31.43	48.05	47.06	81.09	26.1	3.42	2.89	9.97	0.9966	-0.0266	0.9836	-0.0060
KNE	1:3	32.85	49.44	48.49	82.19	22.9	3.86	2.97	9.68	0.9835	-0.0303	0.9893	-0.0064

4. Discussion

The percentage drug content was found to be in the range of 90.00 ± 0.534 to 99.50 ± 0.726 and 94.80 ± 0.104 to 98.80 ± 0.125 for solid dispersions prepared with maltodextrin and HPC respectively. Small SD values indicate that method employed resulted SDs with uniform drug content. The solubility of LUM in 0.1N HCl was found to be 1.762 ± 0.0129M $x10^{-3}$. The solubility of LUM in SDs prepared with Malto at 1:1 ratio was 2.34 ± 0.0016, 4.54 ± 0.0016, 5.03 ± 0.0038M $x10^{-3}$for PM, SE and KNE methods respectively and the solubility of LUM in SDs prepared with maltodextrin at 1:3 ratio was 2.46 ± 0.0024, 4.85 ± 0.0042, 5.15 ± 0.0047M $x10^{-3}$ for PM, SE and KNE methods respectively. The solubility of LUM in SDs ions prepared with HPC at 1:1 ratio was 2.51 ± 0.0053, 4.73 ± 0.0047, 5.63 ± 0.0020$x10^{-3}$for PM, SE and KNE methods respectively. Similarly, the solubility of LUM in SDs prepared with HPC at 1:3 ratio was 2.62 ± 0.0017, 4.84 ± 0.0015, 5.74 ± 0.0056M $x10^{-3}$for PM, SE and KNE methods respectively. In case of PMs, a small increase in solubility of LUM was observed which can be explained due to the formation of a minimum quantity of the dispersion. In case of SDs the solubility was increased with respect to the ratio and method. In all the excipients the saturation solubility was found to be in the order 1:3> 1:1 and methods KNE >SE > PM > Pure drug.

LUM has characteristic peaks at 3579 cm^{-1} (O-H stretching), 2943 cm^{-1} (C-H stretching), 1631 cm^{-1} (C=C alkene stretching), 1582 cm^{-1} (C=C aromatic stretching), 1072 cm^{-1} (C-N stretching), 1011 cm^{-1} (C-O stretching) and 657 cm^{-1} (C-Cl stretching). These characteristic bands were observed in all the solid dispersion systems with slight shifting towards lower to higher wavelength indicates no interaction or mild interaction at molecular level. The results of the dissolution rate studies indicated higher dissolution rate of LUM from SDs when compared to LUM pure form. The DE_{60} values of the SDs that were prepared by the PM, SE and the KNE methods were relatively high when compared with the LUM alone. Overall, the rank order of improvement in dissolution properties of LUM with different polymers, methods and ratios.

- HPC> Maltodextrin
- KNE > SE > PM > Pure drug
- 1:3 > 1:1

One-way ANOVA was used to test the statistically significant difference between pure and prepared solid dispersion systems. Significant differences in the means of DP_{60} and DE_{60} were tested at 95% confidence. The DP_{60} and DE_{60} values of solid dispersion systems prepared by solvent evaporation and kneading method were significantly higher ($P<0.0001$) when compared to DP_{60} and DE_{60} values of physical mixture and pure Lumefantrine.

5. Conclusion

Solid dispersion systems of Lumefantrine were conveniently prepared using maltodextrin and HPC at 1:1 and 1:3 ratios by physical mixture, solvent evaporation and kneading method. The obtained solid dispersion systems were found to be free flowing. With small SD values indicates that method employed resulted solid dispersion systems with uniform drug content. The in vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure Lumefantrine. Mechanisms involved are solubilisation and improved wetting of the drug in the hydrophilic carrier's rich microenvironment formed at the surface of drug crystals after dissolution rate. Finally, it could be concluded that solid dispersion of Lumefantrine using hydrophilic excipients would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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