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Formulation, development and evaluation for combination of lumefantrine and artemether tablets for effective drug treatment of malaria

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ABSTRACT

Aim

To develop various concentrations of excipient formulations and evaluation for combination of two anti- malarial drugs.

Materials and methods

The Lumefantrine and Artemether combination drug-excipients interactions evaluated by pre and post formulation parameters. FTIR by wet granulation method using different concentration of excipients.

Results and discussions

FT-IR clearly indicates that there are no excipients interactions. The pre-formulations showed the values were within the standard limit and post-formulations (LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5) were evaluated for various parameters like weight variation, thickness, hardness, friability, drug content, disintegration and dissolution test. The optimized formulation LUA 4 was found weight variation (mg) 240±0.55, thickness (mm) 3.17±0.09, hardness (n) 74±1.8, friability 0.5%, drug content 96.33% and disintegration time is 1min respectively. The dissolution profile of the optimized formulation LUA 4 tablets revealed that artemether and lumefantrine were released more than 86.75% within 120 mins, 87.60% within 45 mins.The combination of artemether and lumefantrine tablet optimized all batch were of satisfactory stability.

Conclusion

The combination of artemether and Lumefantrine tablet can be considered for treatment of malaria.

Keywords: Artemether, Combination tablet, Excipient concentration, Lumefantrine

INTRODUCTION

Malaria is a major health problem with at least 300 to 500 million people diagnosed with illness every year. In India close to 1.264 million people are at high risk of being infected with malaria. India carries 3% of the global malaria case burden and 2% of global malaria deaths (52% of all malaria deaths outside of sub-Saharan Africa). India also bears 85.2% of the malaria burden in south East Asia, of importance is that India carries 47% of the global *plasmodium vivax* malaria burden, making the country strategically important for global malaria elimination, particularly in the south East-Asian region [5]

Novartis and Medicines for Malaria Venture (MMV) launched Coartem Dispersiblean artemisinin based combination therapy developed specifically for children with malaria. The syrups available in the market are sold under the brand names Gnate-L, Lumether and Zemayl. In the area of novel drug delivery system (NDDS) the artemether-lumefantrine has been formulated as lipospheres, microparticles and nano structured lipocarriers [2]

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Artemether has a rapid onset of action and is rapidly eliminated from the plasma (half life of two to three hours) [8]. Lumefantrine is cleared more slowly and has a longer elimination half life (approximately 4.5 days) [4]. The rationale behind this combination is that artemether initially provides symptomatic relief by reducing the number of parasites present before lumefantrine eliminates any residual parasites. Artemether-lumefantrine also reduces gametocyte carriage and thus should have an impact on malaria transmission [10]. The objective of the present investigation was to develop combination of artemether and lumefantrine tablets. The release characters of the formulations were compared with marketed sample.

MATERIALS AND METHODS

Materials

Artemether and lumefantrine gift samples were collected from Fourrts (India) laboratories Pvt. Ltd, other materials like Micro crystalline cellouse, Hypromellose, Polysorbate 80, were purchased from Welming Pharmaceuticals, India. Croscarmellose, Colloidal silicon dioxide and magnesium stearate were bought from Loba chemicals Pvt. Ltd; Mumbai. Analytical grade of chemicals and reagents were used.

Methods

Pre formulation study

Fourier transform infrared (FTIR) spectroscopy

FTIR analyses were performed on artemether, lumefantrine and formulations (LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5) using a FTIR spectroscopy (Perkin Elmer) by KBr pellet method. All the samples were mixed properly with KBr in 1:3 ratios and were made into pellets. Those pellets were analyzed in over a wave number region of 4000-400 cm^{-1} using FT-IR Spectrophotometer [11]

Angle of repose

It is the maximum angle possible between the tip of the pile and horizontal plane and it was measured by the fixed funnel method. It was measured by following a formula. This test was performed in triplicate [3].

$$\tan\theta = h/r$$

Bulk density

It is the ratio of mass of the blend in bulk volume. It was measured by pouring the powder in measuring cylinder and measuring the volume occupied by powder. This test was performed in triplicate [14]

Tapped density

It is the ratio of mass of the blend to tapped volume. It was measured by digital tap densitometer by measuring the volume occupied by powder after 100 standard tapping. This test was performed intriplicate [14]

Hausner's ratio[13]

Hausner's Ratio = Tapped density / Bulk density

Compressibility index[15]

$C_i = (V_0 - V_f) \times 100 / V_0$
C_i= Compressibility index,
V_o = Bulk density,
V_f = Tapped density.

Formulation procedure of combination tablets

Formulation compositions of combination tablet (240mg) were prepared by wet granulation method. Lumefantrine and microcrystalline cellulose were weighed and shifted through #40 mesh and charged into FBP mixing given for 5 mins. Hypromellose E5 was weighed and dissolved in purified water by using stirrer, is called binder solution. After that polysorbate 80 was weighed and added to the above binder solution. Add binder solution to drymix blend and granulate it FBP, dry the wet granules and LOD to be checked. Remaining chemicals such as croscarmellose sodium, colloidal silicon dioxide and magnesium stearate were accurately weighed and passed through #40 mesh, added to dried granules and mix for 3 mins. Dried granules were shifted through #30 mesh. Dried granules were taken and lubricated by using only the Artemether was passed through #100 mesh, and compressed by using 9 mm flat punch AL embossed on one side and break line on other side.

Post formulation study

Weight variation

Twenty tablets from every composition were weighed one by one and average weight was calculated. Then the individual tablet weights were compared to the average tablet weight. This test was performed in twenty times[16].

Hardness

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 were determined using Erweka hardness tester (Electro labs. India). It was expressed in kg/cm^2. This test was performed in triplicate [12].

Thickness test

Ten tablets were selected randomly in each formulation LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5, thickness was measured by using digital venire calipers (Mitutoyo electro labs, Japan). This test was performed in triplicate[13].

Friability test

Friability of the tablet formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 were measured by using friability tester (Electro Labs EF-2. India). This test was performed in triplicate[6].

Drug content

To ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a Batch[1].

Disintegration test

Disintegration time of the tablet formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 was measured in 1 liter water at 37˚C ± 2˚C using a disintegration tester (Campbell Electronics, Mumbai, India). This test was performed in triplicate[9].

Dissolution studies

In vitro dissolution studies of Artemether

In vitro dissolution studies for all tablet formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 were performed by using USP dissolution test apparatus. (Lab India Pvt. Ltd, India). (Type II, Paddle type, 37˚C ± 0.5˚C) at 100 rpm for 120 minutes. The dissolution medium was used 1000 ml of water. At different time intervals a 10 ml of the sample was taken and analyzed for drug content at 210 nm by HPLC. A 10 ml fresh dissolution medium was added to make the volume after each sample withdrawal[7].

In vitro dissolution studies of Lumefantrine

In vitro dissolution studies for all tablet formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 were performed by using USP dissolution test apparatus (Lab India Pvt. Ltd, India). (Type II, Paddle type, 37˚C ±5˚C) at 100 rpm for 45 minutes. The dissolution medium was used 1000 ml of 0.1 N HCl with 1% benzalkonium chloride. At different time intervals a 10 ml of the sample was taken and analyzed for drug content measure at 335 nm by UV. A 10 ml fresh dissolution medium was added to make the volume after each sample withdrawal [7]

Stability

The formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 were subjected to accelerated stability conditions at 40˚C/ 75˚C% RH and 30˚C/ 65˚C% RH for a period of 1 month. Based on the results of the colour, weight variation, friability, hardness, thickness, disintegration, assay, solubility and dissolution test of all products should be stable in the storage period [7]

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy

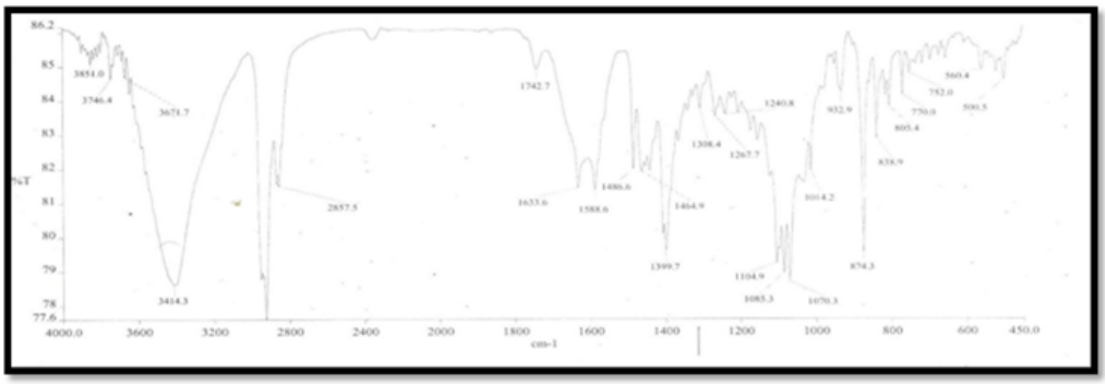

Figure No.1: FTIR spectra for artemether pure

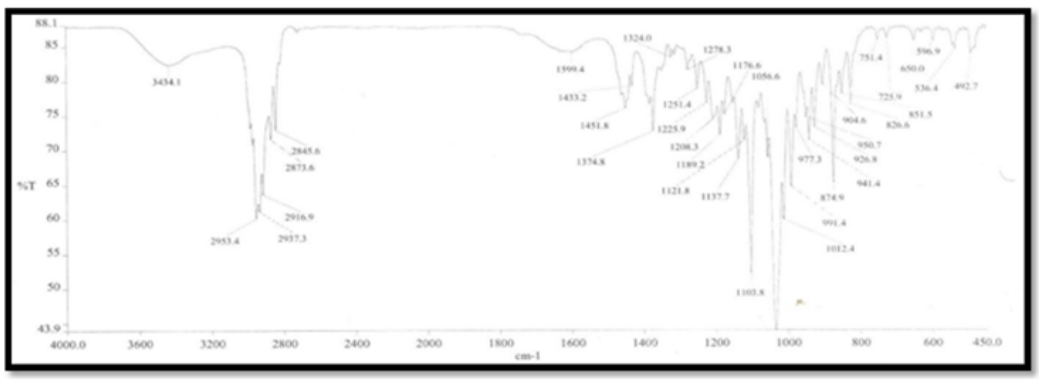

Figure No.2: FTIR spectra for lumefantrine pure drug

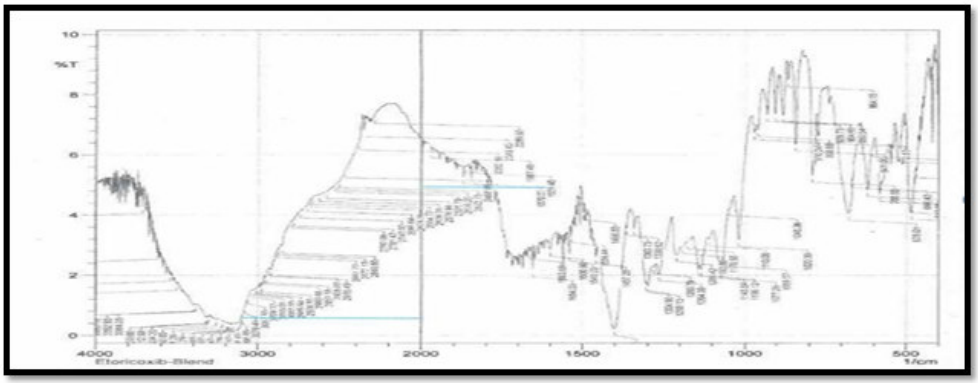

Figure No.3: FTIR spectra for excipients (Without API)

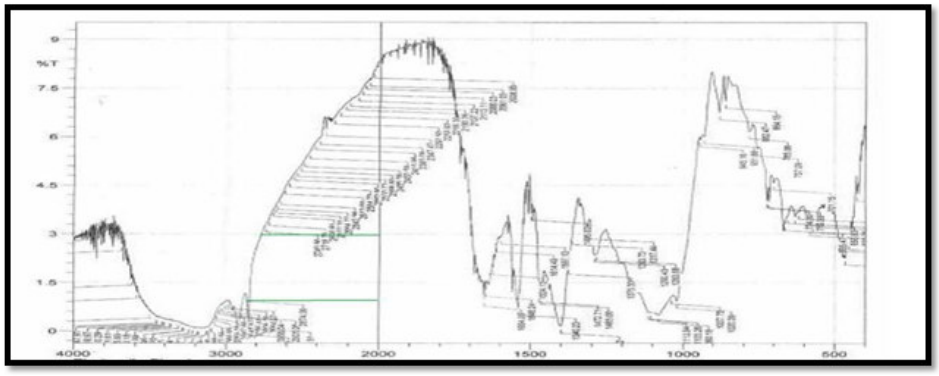

Figure No.4: FTIR spectra for artemether and lumefantrine blend

FT-IR on the selected formulation prepared with different concentration of excipients. The spectrum peak point of the formulation were similar with that of pure drugs of artemether and lumefantrine, it clearly indicates that there are no excipients interaction.

Table No.1: Evaluation flow properties of LUA blend

Formulation code	Evaluation parameter					
	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index	Hausner's ratio	Flowability
LUA 1	43.25	0.5089	0.6694	23.98	1.32	Possible
LUA 2	44.32	0.5091	0.7060	24.57	1.33	Possible
LUA 3	41.40	0.5133	0.7202	23.08	1.28	Possible
LUA 4	39.75	0.5069	0.6459	20.07	1.20	Fair
LUA 5	42.77	0.5129	0.6573	22.50	1.26	Possible

Angle of repose, bulk density, tapped density, compressibility indexand Hausner's ratio of trial formulations LUA 1, LUA 2, LUA 3 and LUA 5 were computed and found that all blends possess possible flow properties. But formulation LUA 4 blend found to be fair flow properties. So LUA 4 blend is better than compared with all trial formulations and hence suitable for direct compression of blends into tablets.

Table No.2: Evaluation of compression parameters

S.No	Formulation	Weight variation (mg)	Average thickness(mm)	Average hardness (n)	Friability %
		Mean±SEM			
1.	LUA 1	241±0.96	3.20±0.09	80±1.2	0.7
2.	LUA 2	239±0.71	3.12±0.09	84±1.5	0.6
3.	LUA 3	242±0.32	3.14±0.09	78±1.7	0.8
4.	LUA 4	240±0.55	3.17±0.09	74±1.8	0.5
5.	LUA 5	238±0.62	3.21±0.09	72±1.6	0.4

The results of all trial formulations (LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5) for weight variation, thickness, hardness and friability were found to be within the standard pharmacopeial limit.

Table No.3: Drug content

S.No	Formulation	Drug content uniformity (%)
1.	LUA 1	92.23
2.	LUA 2	91.67
3.	LUA 3	93.40
4.	LUA 4	96.23
5.	LUA 5	95.33

The results of all trial formulations ((LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5) were found to be 92.23%, 91.67%, 93.40%, 96.23% and 95.33% respectively. The drug content of formulation LUA 4 (96.23%) was found to good drug uniformity content than compared with all trial formulations.

Table No.4: Disintegration test

S.No	Formulation	Disintegration time
1.	LUA 1	3 min 15 sec
2.	LUA 2	2 min 45 sec
3.	LUA 3	2 min 20 sec
4.	LUA 4	1min
5.	LUA 5	1 min 42 sec

Table No.5: Comparative study of different formulations and marketed drug sample (Lumefantrine)

Time (min)	Dissolution test (con/time) %					
	LUA 1	LUA 2	LUA 3	LUA 4	LUA 5	Marketed sample
0	0.00	0.00	0.00	0.00	0.00	0.00
10	45.05	50.40	50.45	50.56	50.50	52
20	55.60	65.34	67.60	58.60	65.40	60
30	65.85	70.55	75.46	75.95	75.47	79
45	70	75	77	87.60	80	87.50

The results of all trial formulations ((LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5) were found to be 3 min 15 sec, 2 min 45 sec, 2 min 20 sec, 1min and 1 min 42 sec respectively. The formulation LUA 4 (1min), exhibits the better disintegration time than compared with all trial formulations.

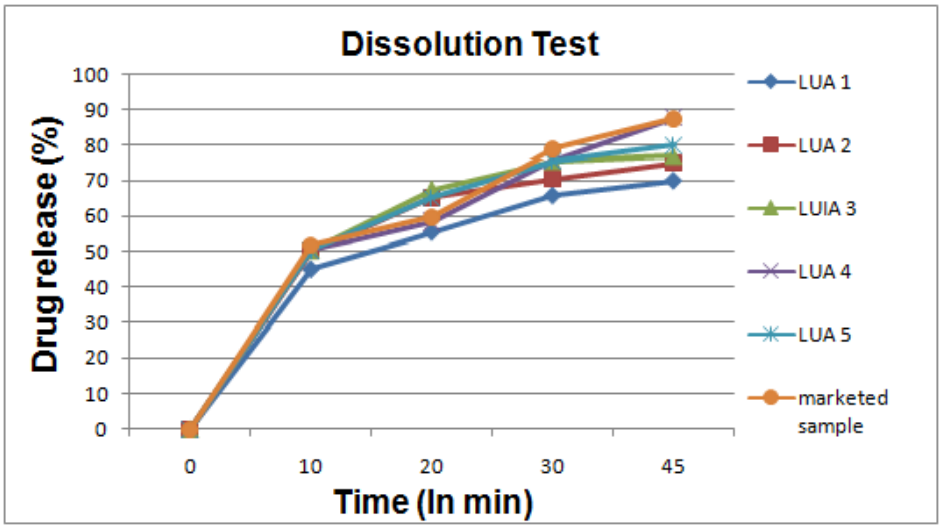

Figure No.6: Comparative study of different formulations and marketed drug sample (Lumefantrine)

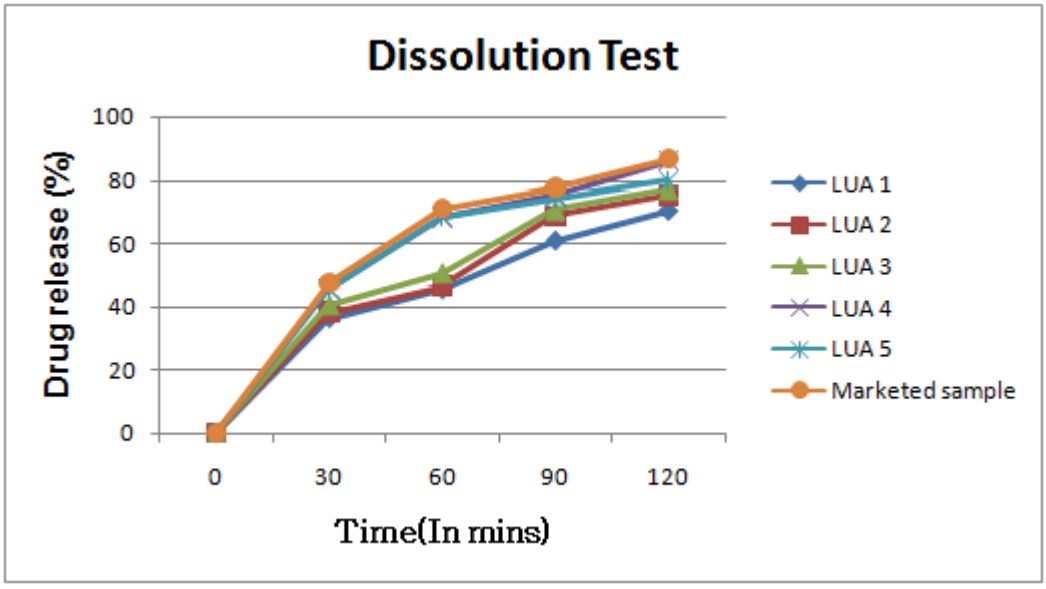

Figure No.7: Comparative study of different formulations and marketed drug sample (Artemether)

The results of all trial formulations (LUA 1, LUA 2, LUA 3, LUA 4, LUA 5 and marketed sample) were found to be 70%, 75%, 77%, 87.60%, 80% and 87.50% in 45 mins respectively. The formulation LUA 4 (87.60% in 45mins) exhibits the better dissolution profile than compared with all trial formulations and marketed drug sample

Table No.6: Comparative study of different formulations and marketed drug sample (Artemether)

Time (min)	Dissolution test (con/time) %					
	LUA 1	LUA 2	LUA 3	LUA 4	LUA 5	Marketed sample
0	0.00	0.00	0.00	0.00	0.00	0.00
30	36.50	38.40	40.50	45.51	45.60	47.30
60	45.60	46.70	50.75	68.50	68.70	71
90	60.65	68.55	70.60	75.30	74.45	77.60
120	70	75	77	86.75	80	86.70

The results of all trial formulations (LUA 1, LUA 2, LUA 3, LUA 4, LUA 5 and marketed sample) were found to be 70%, 75%, 77%, 86.75%, 80% and 86.70% in 120 mins respectively. The formulation **LUA 4 (86.75% in 120mins)** exhibits the better dissolution profile than compared with all trial formulations and marketed drug sample.

Table No.7: Stability result of Artemether and Lumefantrine combination tablet

Daysand storage condition	Formulation	Colour	Weight variation	Friability	Hardness
0 day, 40˚C/75˚CRH & 30˚C/65˚C RH	LUA 1	Yellow	241	0.7%	No change
	LUA 2	Yellow	239	0.6%	No change
	LUA 3	Yellow	242	0.8%	No change
	LUA 4	Yellow	240	0.5%	No change
	LUA 5	Yellow	238	0.4%	No change
30 days, 40˚C/75˚CRH & 30˚C/65˚C RH	LUA 1	Yellow	242	0.8%	No change
	LUA 2	Yellow	240	0.5%	No change
	LUA 3	Yellow	242	0.7%	No change
	LUA 4	Yellow	240	0.5%	No change
	LUA 5	Yellow	239	0.5%	No change

Table No.8: Stability result of Artemether and Lumefantrine combination tablet

Days and storage condition	Formulation	Thickness	Disintegration	Assay	Solubility
0 day, 40˚C/75˚CRH & 30˚C/65˚C RH	LUA 1	3.20%	3 min 15 sec	95.82%	No change
	LUA 2	3.12%	2 min 45 sec	96.21%	No change
	LUA 3	3.14%	2 min 20 sec	97.11%	No change
	LUA 4	3.17%	1min	96.01%	No change

	LUA 5	3.21%	1 min 42 sec	95.22%	No change
30 days, 40˚C/75˚CRH & 30˚C/65˚C RH	LUA 1	3.27%	3 min 30 sec	95.21%	No change
	LUA 2	3.19%	3 min	94.19%	No change
	LUA 3	3.17%	2 min 45 sec	95.15%	No change
	LUA 4	3.17%	1min	96.10%	No change
	LUA 5	3.25%	1 min 50 sec	95.32%	No change

The formulations LUA 1, LUA 2, LUA 3, LUA 4 and LUA 5 showed no significant changes in colour, weight variation test, friability test, hardness test, thickness test, disintegration test, assay, solubility and dissolution of all parameters and stability also stable for a period of 30 days.

CONCLUSION

The combination of artemether and lumefantrine tablet formulation was successfully developed. The pre-formulations showed the values were within the standard limit and post-formulations parameters like weight variation, thickness, hardness, friability, drug content and disintegration time of formulation LUA 4 was showed good results. *In vitro* release profiles of formulation LUA 4 were similar to innovator product. No significant changes were observed in the tablets after the storage period 1 month at 40˚C/75˚C RH and 30˚C/65˚C RH. Hence the study results in the development of artemether and lumefantrine combination tablet comparable to innovator product and fulfilling the objective of the study.

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