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Formulation Development and Evaluation of Artemether 20 MG/Lumefantrine 120 MG Fixed Dose Combination Tablet

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Research Article

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ABSTRACT

Background: Prevailing trends in the global Pharmaceutical sector pose various barriers to Africa's access to essential Pharmaceutical products. Pharmaceutical Research and Development pipelines are running dry. In Tanzania, due to inadequate number of formulation experts and poor technology, the availability of various essential drugs is still inadequate and inconsistent; and this explains why more than 90% the recommended first line drug for treatment of uncomplicated malaria (*Artemether Lumefantrrine*) are imported.

Aim of the study: The aim was to develop a formulation of *Artemether* 20 mg/*Lumefantrine* 120 mg Fixed Dose Combination Tablet.

Materials and methods: This was an experimental study design conducted at Muhimbili University of Health and Allied Sciences, in a Research and Development Laboratory December 2019 to July 2020. A wet granulation method was used by mixing a required amount of Active Pharmaceutical Ingredients (APIs) with a suitable amount of potential excipients. The compression of powder granules was done on a tablet press EKOI 2 (Manufactured in Germany). Evaluation of dissolution profile between the innovator drug and the formulated drug product of this study was conducted; the similarity and differences were calculated as per International Pharmacopoeia. Friability, Disintegration time, Assay and tablets contents uniformity of the formulated drug product are the critical parameters that were also evaluated as per United States Pharmacopoeia.

Results: Tablets were successfully produced with the average weight of

240 mg, diameter 10 mm and thickness of 6 mm. The similarity and difference of 89% and 4.1% respectively were obtained. Friability, Disintegration time, Assay and tablets contents uniformity results were found to be 2 minutes and 29 seconds, Arte-98.1% Lum-99.2%, and Arte-98.0% Lume-101.3% respectively.
Conclusion: The formulated and evaluated drug product of *Artemether* 20 mg and *Lumefantrine* 120 mg fixed dose combination tablet passed the quality requirements as per International Pharmacopoeias and Monographs. Scale up by our local pharmaceutical industry may be done by adopting this formula but should adhere to the official compendia.

INTRODUCTION

Malaria is a common and a life threatening disease which is caused by four different species of Plasmodium: *P.Falciparum, P.Malariae, P.Ovale* and *P.Vivax*. The global effect of the disease threatens public health and impedes the progress of many countries towards prosperity [1].

In 2017, there were estimated 219 million cases of malaria in 87 countries globally. The estimated number of malaria deaths globally was 435, 000 in 2017. In these global cases and deaths of 2017, African regions constituted 92% of malaria cases and 93% of malaria deaths [2].

In Tanzania, according to Tanzania Demographic and Health Survey and Malaria Indicator Survey in 2015-16, Malaria cases raised from 9% in 2011 -12 to 14% in 2015-16. Estimated 6.5 million confirmed outpatient malaria cases were reported in 2016 [3].

The *Artemether Lumefantrine* (ALU) tablet is one of the essential drugs recommended by WHO for treatment of uncomplicated malaria caused by Plasmodium falciparum due to its efficacy, safety and quality. A fixed dose combination of ALU has consistently achieved a cure rate of 95% in clinical trials [4,5].

In Tanzania, the recommended first line drug for treatment of uncomplicated malaria is ALU [6]. Being one of the essential medicines, its availability should be ensured all the time and at affordable prices. However, due to inadequate number of formulation experts and poor technology, the availability and affordability of ALU is still not satisfactory [7,8]. The aim of this study was to develop and evaluate a formulation of *Artemether Lumefantrine* fixed dose combination tablet that has impact of improved availability of this drug.

MATERIALS AND METHODS

Study design and setting

This was an experimental study conducted from December 2019 to July 2020 at Muhimbili University of Health and Allied Sciences (MUHAS) in the Pharmaceutical Research and Development (Pharma R and D) laboratory. This laboratory has a certificate of accreditation ISO/IEC 17043:2010 as a proficiency testing provider in Africa.

Formulation development

By the aid of D-Optimal design expert version 7 software, 8 trial formulations which had different amount of ingredients (Table 1) were produced.

	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Constants	Artemether (%)	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3
	Lumefantrine (%)	50	50	50	50	50	50	50	50
	Magnesium stearate (%)	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
	Polysorbate 80 (milliliters)	4	4	4	4	4	4	4	4
	Colloidal anhydrous (%)	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Variable components	Sodium Lauryl sulphate (%)	1.75	2.5	-	-	-	-	-	-
	Ethanol 96% (milliliters)	35	35	16	10	10	10	10	10
	Water (milliliters)	-	-	20	30	30	30	30	30
	Hydroxypropyl cellulose (%)	0.21	0.42	0.58	0.5	2.0	3.0	3.0	2.4
	Croscamellose (%)	2.5	2.5	3.0	3.0	4.5	5.5	3.0	6.0
	Microcrystalline Cellulose(%)	33.3	32.5	34.4	36.7	30.4	28.3	30.4	28.3

Table 1. Amount of materials for trial formulations.

For each formulation, the powder flow property was evaluated by calculating the bulk density, tapped density, compressibility index and Hausner's ratio according to International and British Pharmacopoeias [9, 10]. Based on scientific knowledge and results for evaluation of powder granules flow property, a wet granulation method was used as the suitable technique in this study.

This stage involved three major steps namely; dry mixing, wet mixing and compression.

Dry mixing: A tubular mixer (Made by Analytical Technology, Bangalore, India) was used to mix for ten minutes the required amount of *Artemether, Lumefantrine* and Microcrystalline Cellulose which were both donated by Keko Pharmaceuticals with the following Lot numbers respectively (Lot number 71963-77 manufactured by Hennan Senyuan Biological Tecnology, in Zhengzhou-China), (Lot number 82186-77-4 manufactured by Hennan Senyuan Biological Tecnology, in Zhengzhou-China), (Lot number 9004-34-6 by Xi'an Henrikang Biotech Co, Ltd). The preparation of binder was done by mixing the required amount of Hydroxyl propyl cellulose which was donated by Zenufa (Lot number 9004-64-2 manufactured by Jiangsu Juming Chemical Technology Co. Ltd) with a polysorbate

80 (donated by Zenufa laboratories, lot number 9005-65-6, manufactured by Aurora Industry Co. Ltd-China) and Ethanol 96% (Techno Pharmchem Bahandurggarh, Haryana, India) so as to solubilize the hydroxyl propyl cellulose. Then a small amount of water (made by Institute of Traditional Medicines at Muhimbili University of Health and Allied Sciences) was added and mixing was done for 2 minutes to make the binder ready for use.

Wet Mixing: This stage involved addition of a binder solution to the mixture of a dry powder. The mixing was done in a mixture granulator machine (Kenwood planetary mixer made in the United Kingdom) for 15 to 20 minutes. Water was added during the mixing until granule formation was attained by a snow ball test. The granules were dried in an oven (Kotternmann 2712 Oven, made in Germany) at a temperature of 50◦C for 16 hours [11]. Then, the required amount of Aerosil which was also donated by Zenufa Laboratories (Lot number 17436, manufactured by Bionique Pharma-India) and Magnesium Stearate (Lot number 557-04-0 Manufactured by Jiangsu Juming Chemical Technology Co., Ltd-China), were mixed with the dried powder granules in a Tubular mixer for ten minutes.

Compression: Production of tablets was done on a single punch compression machine (Tablet press, EKOI 2 made in Germany) where by the upper and lower punches had the size of 10 mm. Eight formulation trial batches were produced with the aid of D-Optimal Design expert version 7 software which ensured the use of appropriate amount of materials to give the acceptable results of friability and disintegration time. The formulated 8 batches were evaluated for their friability, tablet weight uniformity, disintegration time, dissolution and then it was followed by analyzing the tablet API content by using a validated in house HPTLC method with (HPTLC machine (Linomat 5 applicator and CAMAG TLC Scanner 4 both made in Germany [12].

Tablets Quality evaluation

Batches of every formulation were evaluated for their disintegration time, friability, tablets weight variation as per Pharmacopoeia and Monographs [13,14].

Results for tablets evaluation of trial formulations were used in the D-Optimal design expert version 7 to get another 7 predicted formulations that had different amount compositions from the trial formulations as shown in the Table 2.

	Ingredient	F1	F2	F3	F4	F5	F6	F7
Constants	Artemether (%)	8.3	8.3	8.3	8.3	8.3	8.3	8.3
	Lumefantrine (%)	50	50	50	50	50	50	50
	Magnesium stearate (%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Polysorbate 80 (milliliters)	2	2	2	2	2	2	2
	Colloidal anhydrous (Aerosil) in %	1.98	1.98	1.98	1.98	1.98	1.98	1.98
	Sodium Lauryl sulphate (%)	2.1	2.9	-	-	-	-	-
	Ethanol 96% (milliliters)	35	35	10	10	10	10	10
	Water (milliliters)	-	-	30	30	30	30	30

Variable components	Hydroxypropyl cellulose (%)	0.35	0.63	0.21	0.15	1.6	1.04	1.0
	Croscamellose (%)	0.42	0.58	2.4	0.63	1.9	1.46	1.25
	Microcrystalline cellulose (%)	34.17	31.25	35.42	37.5	33.3	32.71	35

Table 2. Amount of materials for predicted formulations.

These 7 predicted formulations were also evaluated for the same parameters as in trial formulations but also assay, comparative dissolution tests (comparison was done with Coartem) and tablets content uniformity were evaluated as per British Pharmacopoeia and International Pharmacopoeias Monographs [15].

RESULTS

Evaluation of the flow ability for the prepared powder mixture

Based on the results presented in Table 3 below, powder granules were found to have good flow properties Because all the tested parameters passed the Pharmacopoeia requirements.

Parameter	Acceptable range	F1	F 2	F3	F4	F5	F6	F7	F8
Bulk density (g/milliliters)		0.47	0.49	0.475	0.483	0.47	0.44	0.40	0.42
Tapped density (g/milliliters)		0.54	0.59	0.572	0.584	0.59	0.53	0.51	0.56
Hausner's ratio (%|)		1.15	1.22	1.21	1.209	1.25	1.20	1.27	1.33
Compressibility Index (% C.I)		16.9	17.67	16.98	17.3	16.9	15.96	17.2	17.01
Acceptance range for % C.I		11 - 25							

Table 3. Results for determination of powder granules flow property.

Tablets quality evaluation for trial batches

The results shown in Table 4 below, shows that formulations number 5 and 6 (F5 and F6) had a long disintegration time compared to other formulations but still all 8 trial formulations passed all the tests as required by United States and International Pharmacopoeias.

Trial formulation	Maximum disintegration time (Min:Sec)	% Friability	Average weight of tablet	RSD of tablet weight
Acceptable range	Not more than 15 minutes	Not more than 1%		Not more than 7.5
F1	2:29	0.5	240.5	1.6
F2	6:35	0.2	236.8	1.73
F3	3:02	0.3	242.3	2.07
F4	5:12	0.23	246.2	1.59
F5	10:17	0.09	242.55	0.66
F6	10:34	0.1	242.65	0.98
F7	5.17	0.3	139.6	1.53
F8	5.21	0.35	243.2	1.02

Table 4. Results for quality evaluation of trial batches.

Results presented on (Table 5) below, shows that all 7 predicted formulation passed the tests as required by Pharmacopoeias.

Trial formulation	Maximum disintegration time (Min: Sec)	% Friability	Average weight of tablet	RSD of tablet weight
Acceptable range	Not more than 15 minutes	Not more than 1%		Not more than 7.5
F1	5:41	0.58	241.8	1.97
F2	5:44	0.4	239.6	1.02
F3	3:21	0.31	247.55	1.17
F4	1:15	0.15	242.04	1.09
F5	2:29	0.45	240.7	1.37
F6	3:21	0.35	241.2	1.30
F7	2:58	0.49	240.4	1.82

Table 5. Results for tablets evaluation of predicted formulations.

By using formulation number 5 in (Table 5) above, three batches were produced and evaluated for comparative dissolution, assay and content uniformity. Based on the Pharmacopoeia and Monographs acceptable ranges, all three batches passed the tests as it is seen in results presented in (Table 6) below.

Similarity (F2) and Difference (F1) of comparative dissolution in Hydrochloric acid media with PH 1.2				Similarity (F2) and Difference (F1) of comparative dissolution in Acetate media with PH 4.5				Similarity (F2) and Difference (F1) of comparative dissolution in Phosphate buffer media with PH 6.8				Assay(%)		Content uniformity	
F2		F1		F2		F1		F2		F1		Art	Lu	Art	Lu
Art	Lu	Art	Lu	Art	Lu	Art	Lu	Art	Lu	Art	Lu				
89.7	85.3	6.3	7.1	93.2	84.1	3.9	3.2	94.2	87.7	4.5	7.9	98.1	99.2	98.1	101.6
Acceptable ranges for F2 is 50% – 100%															
Acceptable range for F1 is 0% - 15% Acceptable range for assay and content uniformity is 95% - 105%															

Table 6. Average results for optimized formulation

DISCUSSION

The study aimed to develop and evaluate the formulation of *Artemether Lumefantrine* fixed dose combination tablet. Based on the results that were obtained in this study, a wet granulation method gave a good flow ability of powder granules which lead to quality tablets with acceptable range of weight variations (rsd) and tablets content uniformity as per British and International Pharmacopoeias. The study has revealed that a wet granulation method is more suitable for development of this kind of drug tablets as it has been shown by other studies [16].

Similarly, as it is shown in different literatures [17], suitable selection of potential excipients and reasonable amount of excipients contributed to the production of tablets that had good disintegration time, dissolution, friability, assay and tablets content uniformity as per Pharmacopoeias and Monographs.

Despite the fact that the study was able to come up with the formulation of *Artemether Lumefantrine* fixed dose combination tablets which is comparable to the innovator drug (*Coartem*), unlike other studies, this study has substituted the use of Alcohol (Ethanol 96% or Isopropyl Alcohol) with distilled water as a solvent for granules formation. The use of alcohol is not very much recommended by WHO due to the fact that it is a class three solvent in ICH Q3 [18], therefore its use should be limited. Also, it is sometimes difficult to get rid of alcohol residuals in the powder granules when Alcohol is used as solvent. Alcohol solvent has advantage over water in the case of powder granules drying time because alcohol takes shorter time compared to water.

The use of distilled water instead of Alcohol, made the formulation of this drug to be cheaper because Alcohol is more expensive and not easily accessible compared to water therefore, the use of water instead of Alcohol makes this study unique compared to other studies.

CONCLUSION

A formulation of Artemether 20 mg/Lumefantrine 120 mg fixed dose combination tablet for treatment of Malaria has been developed and optimized by using a wet granulation method. The optimized formulation used 10 milliliters of Ethanol 10% together with the following percentage weight in a tablet; Artemether 8.3%, Lumefantrine 50%, 2 milliliters of Polysorbate 80, Aerosil 1.98%, Hydroxypropyl cellulose 1.6%, Croscarmellose 1.9%, Magnesium Stearate 2.5% and Microcrystalline cellulose 33.3%.

RECOMMENDATIONS

Scale up by our pharmaceutical industry may be done by adopting this formula but should adhere to the official compendia.

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Author Contributions

Kaswamila-Conception, data collection, analysis and writing. Prof. M. Temu-Supervising, technical advice on data collection writing and manuscript approval. Prof. E. Kaale-Conception, Supervising, technical advice on data collection and manuscript approval. Dr. Betty M.-Conception, writing and manuscript approval. R. Shedafa and P. Tibelinda-Technical support on data collection, writing and data analysis. S. Shemdoe and J.M.Ayubu- Data collection and Writing

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