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Research Article

Comparison of Performance Indices of Artemether – Lumefantrine Fixed Dose Combination Tablets Using Quality by Design Approach I: Physicotechnical Metrics Evaluation

Musibau Aderibigbe Mustapha*, Magnus Amara Iwuagwu, Michael Uwumagbe Uhumwangho

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin. Benin City 300 001, Edo state. Nigeria.
**Correspondence:* musibaumustapha@yahoo.co.uk (Tel.: +234 802 359 8499)

Abstract

Arising from challenges of physicochemical properties of Artemether and Lumefantrine especially their low solubility and permeability, this research was put together to assess the implications on the physicotechnical characteristics of the resultant Artemether-Lumefantrine (AL) fixed dose combination tablets. Granules were prepared by wet granulation technique and compressed into tablets using manually operated tablet press with 12.5 mm; round and flat face punches and die. Compaction behaviours at different compression pressures of between 30 and 42 MNm-2, kinetics as well as mechanisms of dissolution of AL in the tablets were evaluated and compared. Results of compaction characteristics showed that formulation 6 (F-6) was easy to compress into tablets compared with formulation 4 (F-4) with mean yield pressure (Py, MNm-2) of 163.93 and 336.7 respectively. Kinetics of dissolution of artemether in F-4, F-6 and reference product (REF-P) followed Korsmeyer-Peppas model with erosion as mechanism of dissolution in F-4 and REF-P, and Fickian diffusion in F-6. On the other hand, kinetics of dissolution of lumefantrine in F-4 was shown to follow Hixson-Crowell, Korsmeyer-Peppas for F-6 and Zero model for REF-P with all the formulations following Fickian diffusion as mechanism of dissolution.

In conclusion, despite its multi-component nature and strict adherence to design space (DS) component of quality by design (QbD), the physicotechnical properties of the formulations alluded to good performance which will facilitate building of better pharmaceutical quality parameters into final products. This will however be elucidated in subsequent research work.

Keywords: Compression pressure, compaction behaviours, kinetic models, drug release mechanisms, diffusion, erosion.

Introduction

Administration of Artemisinin based Combination Therapies (ACTs) especially artemether and lumefantrine fixed dose combination as a first line treatment in uncomplicated falciparum malarial illness received global acclamation and recommendation [1-2]. In the review of guidelines for its use in 2010, World Health Organization (WHO) posited however, that commercial manufacture of ACTs is fraught with technical problems and other challenges and requested all generic products manufacturers to ensure comparability of their products to the innovator product [3]. The challenges during manufacturing and quality control arose partly from physicochemical properties of the two active ingredients especially their low solubility and low permeability [4].

Successful pharmaceutical dosage forms design, development and commercialization is known to be contingent on a number of factors which pharmaceutical scientists have relentlessly shown to be critical. Such variables in formulation, process and technology have vital roles to play and needed to be properly harmonized if the end product would justify the means [5-6]. Formulation experts have pinpointed the need to synchronize issues of independent process parameters such as type and amount of granulation liquid, granulation time as well as sequence of addition of active ingredients among others [7-8]. In the same vein, formulation variable parameters such as types and quantity of excipients and matrix composition are requested to be properly and scientifically justified. This, it is opined would allow delivery of performance by respective products and enables requirement of fitness for purpose to be met. Other considerations that are required to be taken into account during rational drug design include biological, physical and chemical characteristics of the materials and the products [9-10]. These considerations and others are scientifically handled in DS component of QbD methodology [11-12]; and enabled proactive approach to product design and formulation, processing and commercial manufacture.

This research work was designed to evaluate physicotechnical properties such as compaction behaviours, kinetics and mechanisms of dissolution of AL in optimized F-4 and F-6 and compare with Artelum® (REF-P), a standard, registered and locally manufactured and marketed 40/240 mg Artemether – Lumefantrine fixed dose combination tablets.

Materials and Methods

Materials

The composition of optimized F-4 and F-6 which was within design space was detailed in Table 1 including mode of incorporation of ingredients. The components in both formulations were similar and included Artemether and Lumefantrine (Vital Healthcare, India), Maize starch (Royal Ingredients, Holland), Microcrystalline cellulose (J. Rotten Maier and Sohnne, Germany), Sodium starch glycolate (Rosswell, India), Polysorbate 80 (Irish Country Gold, Ireland), Silicon dioxide (Evonik Degussa, Germany), Magnesium stearate (S. Kant Healthcare, India). They however differed in mode of addition of artemether and lumefantrine and processing methods. All materials were gifts from Edo Pharmaceuticals Ltd, Benin City, Nigeria. Artelum® was purchased from a local community pharmacy in Mushin area of Lagos, south – west Nigeria, and was commercially manufactured in Nigeria.

Methods

Whereas Lumefantrine and other components of F-4 listed in internal phase of Table 1 were mixed, wet kneaded and dried, the excipients in internal phase of F-6 were divided into two and each half was used to prepare granulates of lumefantrine and artemether separately as indicated in the table. During lubrication and blending at external phase, all ingredients were added as listed in the table for F-4 and F-6 and granules were made for tablets compression.

Preparation and compression of tablets

Using manual single punch tablet press (Type F-3, Manesty, England), fitted with round, flat face, 12.5mm die, lower and upper punches with brake score, granules from F-4 and F-6 were compressed into tablets using compression force set at 40 MNm-2 to give hardness of 4 to 8 Kp respectively. Resultant tablets were properly stored for further evaluations.

Assessment of compaction behaviours of optimized F-4 and F-6

Compaction behaviours of F-4 and F-6 were studied by compressing 10 tablets each at different compression forces of 30, 32, 35, 38, 40 and 42 MNm-2respectively. Tablet weight, thickness and radius were determined in triplicate and average estimated to enable calculation of tablet density from equation 1 stated below; radius (r) and thickness (h) are in cm.

$$\text{Tablet density (D)} = \text{Weight (g)} / \pi r2h \quad \text{(equation 1)}$$

$$\text{Ln}\,[1 \div (1\text{-D})] = \text{KP} + \text{A} \quad \text{(equation 2)}$$

Using Heckel plot derived from equation 2, the relationship between compression pressure (P) and tablets density (D) was elucidated by plotting the graph of Ln [1 ÷ (1-D)] versus P. "K" and "A" are constants derived from slope and intercept of the linear portion of the graph respectively. Extrapolation of the constants gave compaction characteristics of the powder as canvassed by other scientists [13-15]. Pharmaceutical properties of disintegration time (DT), hardness and friability were checked to know the effects of increase in compression force on these parameters.

Kinetics and mechanisms of dissolution of AL in formulations

Kinetics and mechanisms of dissolution of the AL in F-4, F-6and REF-P were evaluated by fitting in vitro dissolution data into different kinetic models such as Zero and First order kinetics, Higuchi and Hixson-Crowell, and Korsmeyer-Peppas. Correlation coefficient (R2) was calculated and highest value described best fitted model while "n" value (release exponent) of Korsmeyer - Peppas decided the mechanisms as posited by scientists [16-17]. The following equations were used namely; Zero order: cumulative % drug release vs. time; First order: log cumulative % drug remaining vs. time; Higuchi: cumulative % drug release vs. square root of time; Hixson-Crowell: cubic root of % drug remaining vs. time; Korsmeyer-Peppas: log cumulative % drug release vs. log time, respectively as previously deployed [15].

Results and Discussion

Table 1 contained data about formulation design space for F-4 and F-6 and showed composition as well as stages of addition of each of the components.

Table 1. Formulation design space for optimized F-4 and F-6

Internal: Wet granulation	**Quantity per formulations (%)**		
	F – 4	**F – 6**	
Name of materials		**Lumefantri**	**Artemether**
Lumefantrine	100	100	–
Artemether	–	–	100
Microcrystalline cellulose	87.5	62	33
Maize starch	87	52	35
Sodium starch glycolate	82	47	35
Silicon dioxide	80	66	34
Polysorbate 80	100	60	40
External: Lubrication / blending			
Artemether	100	-	
Microcrystalline cellulose	12.5	5	
Maize starch	13	13	
Sodium starch glycolate	18	18	
Silicon dioxide	20	-	
Magnesium stearate	100	100	

Important parameters that elucidated effects of increase in compression pressure on F-4 and F-6 were shown in Table 2 as Table 3 contained information and data on compaction characteristics as manifested by Heckel plot. Table 4 contained data on correlation coefficient (R2) and release exponent (n); two parameters used to decide kinetics and mechanisms of dissolution of AL in respective formulations.

Formulation design space (DS)

As a core component of QbD, DS for the formulations was constituted as shown in Table 1. The compatibility of the components and suitability of wet granulation as process method were alluded to in the previous research work [18]. It therefore meant that the multidimensional combination of input materials and their interaction with process assured quality of physicotechnical indices of F-4 and F-6 as indicated in this report and espoused by International Conference on Harmonization [19].

Compaction behaviours of optimized F-4 and F-6

Table 3 contained important parameters that characterized the behaviours of F-4 and F-6 formulations during tableting. Indices such as mean yield pressure (Py) which is inversely proportional to constant "K" (i.e. Py = 1/K) derived from the slope of linear portion of Heckel plot and another constant "A", an intercept of the graph - all these parameters indicated the extent to which the formulations were easily compressed into tablets. It was shown that F-6 was easy to compress into tablets given Py value (MNm-2) of 163.93 compared to F-4 with value of 336.7. Constant "A" is a measure of resistance of granules to consolidation during compaction as it represents initial granules consolidation due to rearrangement, original compact volume and initial relative density as opined by researchers [14-15]. This position corroborated findings in this research which showed that F-6 with low value of "A" (1.3868) has low Py value compared to F-4 and therefore consolidated easily when pressure was applied. It may also mean that the granules of F-6 have fewer contact points in the powder bed due to the way it was granulated which made it to have bigger particles that culminated in less opposition to deformation. Comparison of values of "K" and "A" showed that as one increased the other decreases. This characteristic was observed by other researchers to be typical of most multi-component formulations with identical composition as it was the case in this study [13, 20]. Extrapolation and review showed that both formulations had lower R2values. This according to researchers was an indication that both F-4 (R2=0.155) and F-6 (R2= 0.404) undergone consolidation by fragmentation rather than deformation and explained why Py values of both formulations were higher than reported average [13-14].

Table 2. Effects of increase in compression pressure on pharmaceutical parameters

Parameters	Formulations	Compression pressure (P, MNm-2)					
		30	32	35	38	40	42
Friability (%)	F-4	0.77	1.12	0.95	1.16	0.56	0.59
	F-6	1.1	1.13	0.75	2	0.56	0.94
Hardness (Kp)	F-4	3.28	4.55	5.12	4.61	5.37	4.81
	F-6	2.34	2.52	2.03	2.92	4.83	4.94
Disintegration time (s)	F-4	24	24.7	25	21	15	20
	F-6	27.5	33.4	31.9	29.6	31.3	37.3

Table 3. Compaction parameters derived from Heckel plot

Parameters	F-4	F-6
K (slope)	0.00297	0.0061
Mean yield pressure (Py, MNm-2)	336.70	163.93
A (intercept)	1.425	1.387
Correlation coefficient (R2)	0.155	0.404

Kinetics and mechanisms of in vitro dissolution of AL in the formulations

Kinetics as well as mechanisms of AL dissolution from F-4, F-6 and REF-P was elucidated by fitting in vitro dissolution data into various kinetic models. Results in Table 4 which were based on calculation of R2 for all the formulations, indicated that the best fitted model with highest R2 value for dissolution of Lumefantrine was Hixson-Crowell model for F-4 and Korsmeyer-Peppas model for F-6 and zero order for REF-P. Artemether dissolution kinetics in all formulations F-4, F-6 and REF-P followed Korsmeyer-Peppas model respectively. The values of release exponent (n) of Korsmeyer – Peppas model ranged from -0.018 to 0.959 across the formulations indicating that the mechanisms of dissolution were both diffusion and erosion. In particular, mechanisms of dissolution of Lumefantrine in F-4, F-6, REF-P and Artemether in F-6were Fickian diffusion while Artemether in F-4and REF-P dissolved through erosion mechanisms. This assertion was in line with observations of other researchers [6, 16, 17, 20].

Table 4. Data on correlation coefficient (R2) and release exponent (n)

	Lumefantrine			Artemether		
Kinetic Models	**F-4**	**F-6**	**REF-P**	**F-4**	**F-6**	**REF**
Zero order	-0.724	0.192	0.511	0.926	0.853	0.964
First order	0.672	-0.188	-0.553	-0.942	-0.916	-0.972
Higuchi	-0.679	0.181	0.416	0.960	0.935	0.980
Hixson-Crowell	0.685	-0.191	-0.534	-0.943	-0.897	-0.973
Korsmeyer-Peppas	-0.609	0.204	0.260	0.983	0.959	0.994
Release exponent (n)	-0.018	0.008	0.006	0.927	0.354	0.959

Conclusion

Logical mode of incorporation and processing method as provided in the design space of AL formulation had enabled quality physicotechnical characteristics be achieved with consequences that formulations F-4 and F-6 were better in some instances and comparable to REF-P at that level. However, the propensity of the formulations to undergo fragmentation during tableting must be borne in mind during processing so that final tablets will not have high friability. It is also probable that the tablets will be produced at high compression pressure given the Py values of the two formulations.

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Declaration

The authors report no conflict of interest.

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