Journal of PharmaSciTech
ISSN: 2231 3788 (Print)
2321 4376 (Online)
Research Article

Comparison of Performance Indices of Artemether – Lumefantrine Fixed Dose Combination Tablets Using Quality by Design Approach II: Pharmaceutical Characteristics Assessment

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Abstract

Substitution of a pharmaceutical product with another depends among others on the extent of similarity and comparability of pharmaceutical quality parameters of such products. This research work was conceived to evaluate and compare properties of optimized formulations F-4 and F-6 with Artelum® (REF-P), a standard, registered and commercially manufactured Artemether – Lumefantrine (AL) fixed dose combination tablets. Pharmaceutical properties such as weight uniformity, hardness, disintegration (DT), friability and dissolution of F-4, F-6 and REF-P were evaluated and compared. Results of achieved properties were alluded to by process capability index (CpK). Indeed, with weight variation of less than 2% relative standard deviation (RSD), DT of less than 104 s, friability of less than 0.64%, hardness of greater than 4.5 Kp, hardness / friability ratio of greater than 7.7, artemether dissolution in 60 min of greater than 54.5% and lumefantrine dissolution in 45 min of greater than 80%, the pharmaceutical properties of F-4, F-6 and REF-P complied with quality standards that enabled them to deliver good performance as shown by CpK. With DT of less than 2 min and RSD of 0.93% - 1.11%, achieved qualities were better than predefined. It is opined that quality and risk management benefits inherent in quality by design (QbD) model has been brought to bear on F-4 and F-6 as alluded to by the achieved qualities which were in most cases better than predefined and comparable to REF-P.

Keywords: Risks management, dissolution, optimization, process capability, quality index, performance.

Introduction

World Health Organization (WHO) recommended Artemisinin based combination therapies (ACTs) as first line medicines for treatment of uncomplicated malaria caused by P. falciparum and backed it with treatment guidelines in 2006 with a review and revision in 2010 [1-2]. A core component of these ACTs is Artemether and Lumefantrine (AL) which is meant to be administered in fixed dose combination of ratio 1: 6 of Artemether and Lumefantrine respectively. In its conclusion of a survey conducted on the quality of antimalarial circulating in Sub-Saharan Africa, WHO reported that about 28.5% of such drugs (ACTs being 53%) failed to meet internationally acceptable quality standards, 11.6% of which may have health implications [3]. The problems of low solubility and low permeability of both artemether and lumefantrine compounded the challenges faced by pharmaceutical formulation scientists during manufacturing and quality control of resultant fixed dose combination products [4]. Resolution of these physicochemical problems as well as considerations for other issues are scientifically handled in QbD approach [5-6], which lead to proactive building and designing of quality into formulation, processing, manufacture and final products. Compliance with regulatory guidelines and requirements, better understanding of risks associated with inputs, process and finished products, risks mitigation and contingency plans to address them throughout product lifecycle were also enabled by QbD [7].

This research work was conceived to evaluate and compare pharmaceutical properties of optimized formulations F-4 and F-6 with Artelum® (REF-P), a standard, registered and commercially manufactured and marketed 40/240 mg Artemether – Lumefantrine fixed dose combination tablets. Such pharmaceutical properties as dissolution and disintegration time, hardness and friability and weight uniformity were assessed to allude to their comparability and interchangeability.

Materials and Methods

Materials

The tablets evaluated in this research work were produced as reported in part I of this article; and composed of 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). All materials were gifts from Edo Pharmaceuticals Ltd, Benin City, Nigeria while Artelum® was purchased from a community pharmacy in Mushin area of Lagos, south-west Nigeria.

Evaluation of tablets of optimized F-4, F-6 and REF-P

During tablets compression, weight variation was monitored using Ohaus precision balance (Ohaus, Japan). 10 tablets were singly weighed, average determined and both standard deviation (SD) and %RSD were calculated and recorded. Hardness (crushing strength) of the tablets was determined using hardness tester (Model HT- 30/50, Campbell Electronics, India). Diametral compression force of 5 tablets was singly determined, mean and standard deviation of the values computed. By means of Erweka friability tester (Erweka, Germany), friability of 10 tablets was evaluated. Weight of 10 tablets was determined before the test (Wb), and sample fed into friability tester which was rotated for 100 revolutions at speed of 25rpm for 4 min. Tablets samples were carefully removed, dusted and the weight rechecked after the test (Wa). Percentage friability was calculated as shown in equation 1 for 3 replicates and mean and standard deviation computed and recorded.

$$\% \text{ Friability} = (Wb - Wa) \div Wb * 100 \quad \text{(equation 1)}$$

Disintegration time was evaluated with a disintegration apparatus (Manesty, England). One tablet each was put in each of the tubes and hung on the apparatus to which container water at temperature of 37 $\pm$ 1oC has been added. The apparatus was switched on and the time it took each tablet to completely break down into particles small enough to pass through predetermined aperture of the mesh was determined. Average and standard deviation were also estimated.

Evaluation of in vitro dissolution of F-4, F-6 and REF-P

Using USP dissolution apparatus (Elecrolab, USA), with paddle (apparatus II) rotating at 100rpm to which vessel has been added 900ml of dissolution medium made up of 1% Benzakonium chloride in 0.1M hydrochloric acid thermo stated at 37 ± 0.5^{0}C; one tablet each was placed in each vessel and the apparatus switched on. Samples of 2ml were collected at 5, 15, 30, 45, 60, 75, 90 and 120 min respectively and filtered with 0.45µm size PTFE membrane filter. Samples were spiked with 20µg/ml Nevirapine internal standards (IS) and analysis carried out using HPLC system (model ChemStation, Agilent technology, Japan). Each of the test solutions was run at 216 nm wavelengths at ambient temperature; injection volume of 20µL with flow rate of 1.0 ml per min, mobile phase of acetonitrile / 25mM potassium dihydrogen phosphate (70:30)% and column of Zorbax XDB C8 150 x 4.6mm, 5µm. Results were collated, analyzed and recorded. 2ml samples withdrawn were replaced with equal volume of dissolution medium. Quantity of AL in samples was extrapolated from equation of line of best fit drawn from calibration curve.

Calibration curve

Calibration curve solutions were prepared from AL reference sample (RS) in various concentrations of 62.5/375, 125/750, 187.5/1125, 250/1500, 375/2250, 500/3000 and 750/4500µg/ml respectively using solution of tetrahydrofuran / acetonitrile (50:50)%. By following above stated chromatographic method, data were collected that enabled calibration curves to be plotted and used to estimate quantity of AL in samples collected during dissolution testing.

Process capability index (CpK)

As this study involved processing techniques, CpK was calculated as shown in equations 2 and 3 for some CQAs with a view to know how well the process especially tablet compression is in control of delivering quality at all times and for all necessary parameters. A CpK value of greater than 1 is adjudged to be an indication of a better process performance [6].

Process capability index (CpK) = (X - LSL) ÷ 3s (equation 2)

Process capability index (CpK) = (USL - X) ÷ 3s (equation 3)

(X is sample mean, LSL is lower specification limit, USL is upper specification limit, s is standard deviation; Equation 2 is used when X is lower and Equation 3 when X is higher than specification average, respectively).

Results and Discussion

Predefined quality targets and achieved pharmaceutical qualities as well as values of CpK of some CQAs of the formulations were listed in Table 1. Figure 1 showcased the dissolution profiles of AL in each of formulations F-4, F-6 and REF-P and the extent to which they are comparable.

Quality target and product profile (QTPP)

As a prerequisite of QbD, QTPP was established on the basis of science and risks associated with critical material attributes (CMAs) and design space. As shown in Table 1, some of the quality targets are considered critical as their variation may negatively impact the overall critical quality attributes (CQAs) of final product. These quality parameters were properly monitored during processing.

Pharmaceutical properties of optimized F-4, F-6 and REF-P

The pharmaceutical properties of optimized formulations F-4 and F-6 are better than predefined and indeed, the results of hardness and friability, weight uniformity and DT as well as dissolution as shown in Table 1 are comparable to those of REF-P. In particular, the tablets weight (g) varied from 0.5369±0.005 (F-4) to 0.5387±0.006 (F-6) and 0.4575±0.009 (REF-P) with relative standard deviation (RSD) of 0.93%, 1.11%, and 1.95% for F-4, F-6 and REF-P respectively. It could be inferred that weight variation was drastically minimal and within specification of less than 5% specified in compendia [8]. During risks assessment, tableting process was adjudged to pose high risk to weight uniformity; with results of RSD, it was shown that proper monitoring of tablets weight as a CQA was upheld. This minimal weight variation engendered optimal content uniformity of actives in the final tablets.

Hardness values of F-6 and REF-P as indicated in Table 1, presupposed that the tablets are strong enough to withstand both normal and abnormal stresses during handling at any point in the value chain of manufacturing and distribution.

Table 1: QTPP and summary of achieved pharmaceutical properties of F-4, F-6 and REF-P

Properties of tablets	Targets	F – 4	F – 6	REF – P
Mean weight (g, n=10, ±SD , %RSD)	RSD of ± 5%	0.5369 ± 0.005 0.93	0.5387± 0.006 1.11	0.4575± 0.009 1.95
Mean hardness (Kp, n=5, ±SD); CpK	4 – 8 Kp ≥ 1	4.93 ± 0.2 1.55	5.98 ± 0.71 0.93	5.56 ± 0.54 0.96
Mean disintegration time (s, n=6, ±SD); CpK	≤ 15 min ≥ 1	53.57 ± 12.24 23.1	58.32 ± 8.39 33.4	103.33 ± 5.39 49.3
Mean friability (%, n=5, ±SD); CpK	≤ 1 ≥ 1	0.635 ± 0.16 0.76	0.261 ± 0.10 2.46	0.473 ± 0.32 0.55
Hardness/friability ratio (HFR)	≥ 4	7.76	22.91	11.75
Dissolution (%, n=3, SD): Artemether Lumefantrine	≥ 40% in 60 min	73.32 ±18.7	65.03 ±8.36	54.58 ±2.31
	≥ 60% in 45 min	92.22± 5.48	80.06±13.86	90.03±1.39

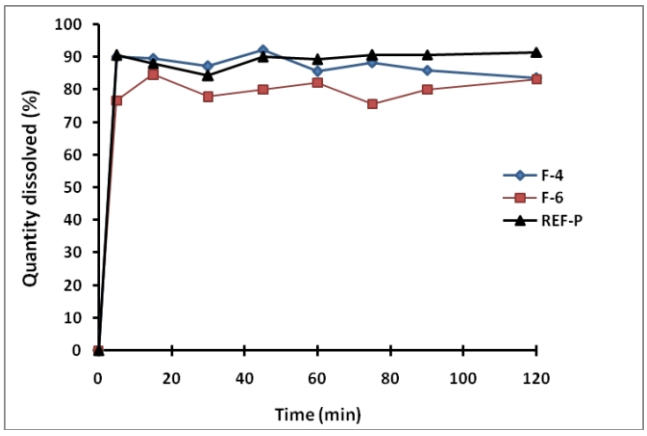
The target set for CpK is ≥1 in all parameters of DT, hardness and friability [6].

With friability values all of which were lower than 1% maximum official specification; and hardness / friability ratio of ≥7.7, it could be inferred that the tablets are strong enough to remain intact throughout their life cycle as observed by other researchers [9-10]. In spite of high hardness/friability ratio which is a good criterion of mechanical strength, results of evaluation of DT as shown in Table 1 did not in any way indicate adverse effects on it. With DT values of less than 1 min in F-4 and F-6, it was evident that timely disintegration of tablets occurred and led to swift and rapid dissolution than REF-P with DT of about 1.7 min.

The dissolution of Artemether in F-4, F-6 and REF-P at 60 min was in line with recommendation as shown in Table 1. Although there are no compendia specification ranges, WHO used ranges of not less than (NLT) 40% or 60% in 60 min or 180 min respectively for Artemether and NLT 60% in 45 min for Lumefantrine in its QAMSA study [3]. The dissolution of Lumefantrine was not in any way hampered as F-4, F-6 and REF-P recorded values that were higher than 60% recommended in 45 min as shown in Table 1. All characterization indices deployed in this study to evaluate process and product performance viz a viz weight uniformity and hardness, friability and DT and dissolution were duly recommended by other researchers [11-13].

The dissolution results presented as dissolution profiles in Figure 1 were derived from extrapolation of peak areas of chromatograms at different sampling time using equation of line of best fit gotten from calibration curves of Artemether and Lumefantrine reference standard (RS). Prompt dissolution was shown by Lumefantrine in all the formulations and REF-P while release of Artemether was slow. In the first 5 min, dissolution rate of Lumefantrine was high across the formulations including REF-P. Slow dissolution behaviours of Artemether are attributable in part to its low solubility and low concentration in the fixed dose combination which engendered poor signal detection and capture by analytical instrument and resulted in slow quantitation. Lack of chromophore in Artemether contributed to the problem and hampered efficient quantitation. Dissolution medium could also be a source of problem of artemether evaluation because of its instability in such media and inclusion of Benzalkonium chloride is not an exception as previously reported [14].This problem may linger on until a dissolution medium is recommended in compendia for evaluation of Artemether especially in a fixed dose combination.

From analysis of variance (ANOVA) using Microsoft Office Excel, the significance of difference in variances of Artemether dissolution in F-4 and F-6 compared to REF-P was expressed by F-test values of 0.562 (F-4) and 0.556 (F-6). Similarly, the level of difference in variances of Lumefantrine dissolution in F-4, F-6 compared with REF-P was to the extent of F-test values of 0.611 (F-4) and 0.418 (F-6). Comparison of dissolution characteristics of F-4 and F-6 with that of REF-P using Student's t-test showed that the dissolution patterns of Artemether



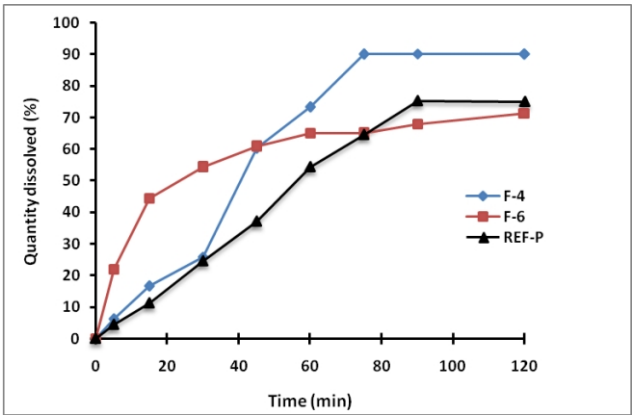


Figure 1. Dissolution profiles of Lumefantrine (A) and Artemether (B) in formulations

component of the formulations were statistically different having returned p-values of 0.003 for F-4 and 0.026 for F-6. With p-values of 0.141 for F-4 and 0.00012 for F-6 on dissolution characteristics of Lumefantrine component, it was evident that, while there was no statistically significant difference in dissolution between F-4 and REF-P, the same could not be said of F-6 as the difference was significant because its p-value of 0.00012 was less than 0.05.

As part of focus of this study was on process variables especially consequences of mode of incorporation and sequence of processing of AL, CpK which is a measure of capability of process to deliver within defined specification limits, was engaged to show to what extent CQAs of final output have been achieved. Values above 1 are indications that products from such process are less likely to be out of specification ranges as experts opined that CpK value of 1.33 is equivalent to a 4 sigma level of process performance when using 6 sigma standards [6]. Guided by the results shown in Table 1 it was evident that the process has not been in full control of some parameters especially friability and hardness. Values of less than 1 were indications of suboptimal process and such must be properly monitored to avoid out of specification results as is most likely in friability of F-4 and REF-P, and hardness of F-6. Formulations with observed CQAs having values of above 1 implied that the process as optimized was in control and have the capacity to remain in control to deliver quality performance over a long period of time as remarked by experts [6, 15]. This characteristic was demonstrated by DT of all formulations with CpK values ≥23.

Conclusion

Rational handling of combination and processing of AL formulations had enabled QTPP to be achieved better than predefined with consequences that formulations F-4 and F-6 were better in some instances and comparable to REF-P.For example DT of less than 1 min and RSD of 0.93% (F-4) and 1.11% (F-6) were achieved against predefined DT of less than 15 min and RSD of ±5% for weight uniformity. Given DT of 53.57 s (F-4), 58.32 s (F-6), these formulations could be developed as soluble / dispersible / rapid disintegrating tablets to be used as alternatives to dry powder for paediatric suspension. It is thus posited that scientific as well as risk management basis of these formulations had led to quality outcomes from F-4 and F-6 as alluded to by the achieved pharmaceutical properties.

Acknowledgements

The authors wished to recognize the support received from colleagues in the pharmaceutical industry. Indeed, we are thankful to management of Edo Pharmaceuticals limited, Benin City, Edo state, Nigeria for its generosity towards this research work.

Declaration

The authors report no conflict of interest.

References

[1] World Health Organization. Guidelines for the treatment of Malaria.1st edition. Geneva, WHO.[Online] 2006; Available at: www.who.int/malaria/docs/ Treatment Guidelines 2006.pdf. Accessed on 18 January 2014.

[2]. World Health Organization. Guidelines for the treatment of Malaria.2ndedition. Geneva, WHO press, pdf document 2010: 1 - 210.

[3]. World Health Organization. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa (QAMSA study report).Geneva, WHO, Department of Essential Medicines and Pharmaceutical services 2011.

[4]. Fule R, Meer T, Sav A, Amin P. Solubility and dissolution rate enhancement of Lumefantrine using hot melt extrusion technology with physicochemical characterization. Journal of Pharmaceutical Investigation 2013; 43:305–321.

[5]. Nethercote P, Ermer J. QbD for Analytical methods: Implications for method validation and transfer. Pharmaceutical Technology 2012; 74-79.

[6]. Weichbrodt N, Camalo M. Using Quality by design to optimize tech transfer of advanced sterile processing. Pharmaceutical Manufacturing 2012; 3-7.

[7]. Migliaccio G. The impact of Quality by Design (QbD) on manufacturing and product quality-innovator Industry perspective. Pfizer Global Supply [Online] 2011; 34-54. Available at:www.fda.gov/downloads /AboutFDA/CentersOffice/CDER/.Accessed on 15 June 2013.

[8]. The International Pharmacopoeia. 4th Edition. CD-ROM. Geneva, WHO Department of Essential Medicines and Pharmaceutical Policies, 2008.

[9]. Odeku OA, Awe OO, Popoola B, Odeniyi MA, Itiola OA. Compression and mechanical properties of tablet formulations containing corn, sweet potato, and cocoyam starches as binders. Pharmaceutical Technology 2005; 82-90.

[10]. Mustapha MA, Aluya QA,Ihunde JE.Formulation development and quality profiling of paracetamol – ibuprofen combination tablets. Int J Pharm Sci Res 2014; 5: 964-69.

[11]. Kannan V, Kandarapu R, Garg S. Optimization techniques for the design and development of novel drug delivery systems, Part 1. Pharm. Tech 2003; 2: 74-90.

[12]. Mustapha MA, Igwilo CI, Silva BO. Performance equivalence study of sodium starch glycolate, modified maize starch and maize starch as disintegrants in paracetamol tablet formulation. Medical Journal of Islamic World Academy of Sciences 2010; 18: 61–67.

[13]. Biswas R, Basak SC, Shaikh Sa. Formulation development and polymer optimization for once-daily sustained release matrix tablets of domperidone. Journal of PharmaSciTech 2011; 1:28-34.

[14]. Umapathi P, Ayyappan J, Quine SD. Development and validation of adissolution test method for Artemether and Lumefantrine in tablets. Tropical Journal of Pharmaceutical Research 2011; 10: 643 – 653.

[15]. Mustapha MA. Formulation and process optimization of Artemether-Lumefantrine fixed dose combination tablets using Quality by Design approach. PhD Thesis (Pharmaceutics and Pharmaceutical Technology), University of Benin, Nigeria.December, 2014; pp 152.