INNOVARE JOURNAL OF SCIENCES

Vol 3, Issue 2 , 2015

ISSN: 2321-5496

Original Article

COMPATIBILITY AND PROCESSING METHODS STUDY OF FORMULATION OF ARTEMETHER–LUMEFANTRINE FIXED DOSE COMBINATION USING ANALYTICAL TOOLS

MUSIBAU A. MUSTAPHA*, MAGNUS A. IWUAGWU, MICHAEL U. UHUMWANGHO

Department of Pharmaceutics and Pharmaceutical Technology. Faculty of Pharmacy. University of Benin. Benin City 300 001, Edo state. Nigeria. Email: musibaumustapha@yahoo.co.uk

Received: 20 January 2015, Revised and Accepted:25 February 2015

ABSTRACT

Objective: This study was undertaken to devise the best way to incorporate artemether-lumefantrine (AL) as model drugs during processing without compromising quality.

Methods: Utilization of analytical tools revealed how compatibility of formulation components and suitability of process methods were monitored and controlled to achieve quality outcome. Excipients of proven performance in wet granulation method as well as AL as model drugs were designed into six formulations coded F-1 to F-6 to reflect modes of incorporation. Physical mixtures and wet granulated samples at different levels of processing were screened as in-process materials for compatibility and method suitability using Fourier Transform Infrared (FTIR), Differential Scanning Calorimetry (DSC) and High Performance Liquid Chromatography (HPLC) techniques. Assessment of potential risks inherent in formulation and process unit operations was adequately addressed by these instruments.

Results: Matching spectra, thermograms and chromatograms at different levels of processing indicated that there were no disappearance of old or appearance of new spectral bands; showed reduction of melting endotherm and similar characteristic elution times of AL as they transformed from pure material to physical mixture (PM) and to granules.

Conclusion: Results from this work alluded to compatibility of formulation components and process method suitability to the extent that the resultant granulates were good enough for further processing.

Keywords: Critical quality attributes, materials attributes, melting endotherm, quality by design, retention times, wet granulation.

INTRODUCTION

Formulation scientists and other researchers put AL in class IV of biopharmaceutics classification system (BCS) [1, 2]. This implies low solubility, low permeability of the two actives which are challenges that must be properly addressed during formulation, development and manufacturing if the product must deliver good performance as anticipated by World Health Organization (WHO) in its guidelines on malaria treatment using Artemisinin-based Combination Therapies (ACTs) [3- 5].

Utilization of process analytical technology (PAT) tools and devices in evaluation of compatibility of formulation components and suitability of process method had been reported in literature. Indeed, Fourier Transform Infrared (FTIR) and High Performance Liquid Chromatography - HPLC, (both non-thermal) and Differential Scanning Calorimetry- DSC (thermal) techniques have been engaged by various researchers in this direction. For example, the compatibility of flutrimazole with formulation components such as Eudragit RS 100, sodium lauryl sulfate, polyvinyl alcohol, paraffin and stearic acid was confirmed by using DSC and FTIR [6]. Other researchers utilized the instruments and found that ezetimibe was compatible with sodium starch glycolate, microcrystalline cellulose, silicon dioxide, starch and polyethylene glycol (PEG) 400 when formulated and processed as tablet dosage form [7]. By indicating the formation of solid dispersion without chemical interaction among simvastatin, mannitol, soy polysaccharide and cyclodextrin polymers, the utility of FTIR spectroscopy in potential risk assessment and compatibility evaluation was demonstrated while also confirming the suitability of the process method used in solid dispersion [8]. As one of the most widely used PAT sensors, FTIR spectrometer was engaged by researcher who concluded absence of interactions in solid state between PEG 6000 and cyclosporine [9]. In the same vein, application of FTIR spectroscopy showed a slight shift in characteristic peaks when juxtaposing the spectra of pure valsartan, microcrystalline cellulose, sodium lauryl sulfate and their blends but it was concluded that all the materials were compatible because the overall spectrum has no differences [10]. The observation that IR spectroscopy is fast becoming an important analytical tool in pharmaceuticals validation was reaffirmed by researchers when they utilized FTIR spectrometer to allude to process method suitability and performance [11, 12].

Application of wet granulation method in the preparation of granules for solid dosage forms such as tablets, capsules, dry powder for suspension and a host of others is as old as history of pharmaceutical manufacturing itself. The method enabled incorporation of active(s) as well as many other excipients as may be required for the production of free flowing and compressible granules which engendered uniformity of contents and weight; and consistency in active ingredient among others [13]. Adoption of wet granulation method according to formulation scientists offered many opportunities and promises for a better outcome as variously described which includes its assurance of drug homogeneity, reduction in dust level during processing, increase in wetability and powder consolidation; others include stoppage of agglomeration and improvement in flowability and tabletability of starting materials [14, 15]. Drug formulation researchers have shown that wet granulation process variables such as granulation time otherwise known as granulation end-point determination, type and amount of granulation liquid, sequence of addition of materials especially active ingredient(s) as well as wet milling using different sieve sizes (i.e. granules size) are central to successful wet granulation process.

This is because these variables as enumerated have been implicated in varying granules appearance, size and shapes, dustiness, segregation during mixing, densities and flowability characteristics [16].

This research work was designed to develop and characterize in-process materials of AL fixed dose combination (AL FDC) formulation with emphasis on evaluation of mode of incorporation of AL into the formulations; process method suitability and formulation components compatibility. With focus on 40 / 240 mg strength, it is expected that adoption of concept of building quality into product right from onset will throw more light on knowledge and understanding of processing characteristics that are required to ensure overall quality of AL FDC formulation.

MATERIALS AND METHODS

Materials

In addition to lumefantrine and artemether (Vital Healthcare, India), other materials used include maize starch (Royal Ingredients, Holland), microcrystalline cellulose (J. Rotten Maier and Sohnne, Germany), silicon dioxide (Evonik Degussa, Germany), sodium starch glycolate (Rosswell, India), polysorbate 80 (Irish Country Gold, Ireland), and magnesium stearate (S Kant Healthcare, India). All these pharmaceutical grade materials were provided by Edo Pharmaceuticals Ltd, Benin City, Nigeria and used as such.

Methods

Formulation design space (DS)

Identical formulations F-1 to F-6 were designed to comprise in addition to 43.62% lumefantrine and 7.27% artemether, other components of 4.18% maize starch, 21.82% microcrystalline cellulose, 0.91% silicon dioxide, 20% sodium starch glycolate, 1.82% polysorbate 80 and 0.38% magnesium stearate. The design of formulation composition as above and as shown in **Table 1** was contingent upon physicochemical properties of artemether and lumefantrine, which must be properly gauged so that the final product performs as intended. Hence, excipients of proven performance such as sodium starch glycolate, microcrystalline cellulose and maize starch were used as disintegrants and diluents; silicon dioxide utilized as binder and glidant to reduce the sticking propensity of lumefantrine. Polysorbate 80 was used as surfactant to improve disintegration and dissolution and magnesium stearate was added as lubricant. Although the compositions of formulations are similar, they were processed in 5 different ways including a placebo formulation as shown in **Table 1.**

Preparation of physical mixtures (PM) and granules

Accurate quantities of artemether and lumefantrine (AL) were weighed with analytical balance (Ohaus Corporation, USA) as contained in DS and in the ratio they will appear in final granules and manually triturated using mortar and pestle. In the same way, physical mixtures of all excipients and all starting materials (excipients + actives) and binary mixture of AL were separately prepared and kept aside for further evaluation. Using wet granulation method, formulation granulates were prepared by following the processes outlined in **Figure 1** with incorporation of AL as indicated in **Table 1**. Each component was accurately weighed and manually pressed through 1mm sieve to remove lumps. Respective components were added to the mortar and triturated to achieve homogenous wet mass which was manually pressed through 3 mm sieve. Wet granules were spread on trays and dried in hot air oven (Manesty-Mitchell, England) at temperature of 55^{o}C until moisture content was 2.2% determined with moisture analyzer (Ohaus, China); dried granules were manually pressed through sieve 2 mm and together with other excipients as contained in DS were mixed together and then properly stored for further evaluation.

Assessment of compatibility and processing methods suitability

In line with sampling plan shown in **Table 2**, assessment of compatibility of formulation components and method suitability was performed using FTIR, DSC and HPLC instruments.

FTIR testing procedure involved preparation of potassium bromide (KBr) pellet from samples listed in **Table 2**. For each of the samples 3 mg was accurately weighed with 200 mg of KBr using analytical balance (A N D, GR-200, Germany) and triturated in a small glass mortar with pestle. The powder blend was compressed into KBr pellet using pellet press and was fixed onto sample holder. The sample preparation followed the compressed alkali metal halide pellet (KBr pellet) method. Using FT-IR spectrometer (Spectrum BX, Perkin Elmer, Germany), configured with Spectrum software (version 5.3.1, Germany), the background was first scanned after which the sample holder carrying KBr pellet was fixed on the interferometer and scanned over 350 – 4000 cm^{-1} range. The spectrum of each sample was recorded and displayed on the monitor, all the peaks were duly labeled automatically and some manually. By analyzing and matching the information from spectrum with the database of compounds, different chemical compounds were identified and listed out. Sample of Polysorbate 80 was prepared by putting a drop in a glass slide and evenly spread. KBr was not used. The slide was fixed onto sample holder and thereafter followed similar process as in powder samples. This process was repeated for all samples listed in **Table 2**. The quantity of each starting material in the physical mixtures, and granules was in the ratio it will appear in the anticipated final formulation.

Test samples for DSC screening were prepared by weighing approximately 2 mg of each sample as in **Table 2**, and poured into a standard aluminum pan with pierced lid. Using DSC apparatus (Netzsch DSC 204 F1 t-sensor/E, Netzsch, Germany), thermograms of test samples were taken under nitrogen purge at flow rate of 70ml / min; heating rate of 10^{o}C / min, and scanned over a temperature range of 20 - 400^{o}C ; and empty pan was used as reference. Thermograms were labeled to show peak maximum temperature, peak area which represents the enthalpy of fusion / transition. By matching thermograms at different stages of processing, the thermal behaviour of samples as well as any interaction was pinpointed. Chromatography evaluation of samples as indicated in **Table 2** was carried out with HPLC system (model ChemStation, Agilent technology, Japan; column: Zorbax XDB C8, 150x4.6 mm, 5 µm; mobile phase: acetonitrile/25mM potassium dihydrogen phosphate 70:30). Samples of reference standard (RS) as well as test samples (TS) of equal strength were prepared using about 10 ml of solution of acetonitrile and tetrahydrofuran (50:50%) to have a concentration of 250 / 1500 µg per ml of AL. The solutions were respectively sonicated for 10 min to dissolve the content and then filtered through 0.45µm size PTFE membrane filter. Each of the test solutions was run at 216 nm wavelength at ambient temperature; injection volume of 20 µL with flow rate of 1.0 ml per min. Results were collated, analyzed and recorded. The chromatograms developed at different stages were compared and matched with the chromatogram from reference standard to detect any incompatibility and unsuitability in the formulation and process method respectively.

Assessment of potential risks to CQAs of granules due to processing methods

The risks associated with CQAs due to process unit operations especially wet mixing and wet milling, drying and dry milling were assessed for probability, severity and impact. Samples of granules were taken at different levels and tested to allow assessment of effects of processing on compatibility and stability of granulates. This was done using instrumentality of FTIR, DSC and HPLC. This provided for early detection and prevention/ mitigation of risks at development stage as envisaged from processes.

RESULTS AND DISCUSSION

FTIR screening

Figures 2-3 and Table 3 adequately addressed the risks envisaged from materials incompatibility and unit operations within the process method especially wet kneading and drying at high temperature (50 – 55^{o}C). Comparison of spectral images of artemether and lumefantrine with the spectrum of their binary mixture showed no disappearance of major old peaks neither were there appearance of new ones.

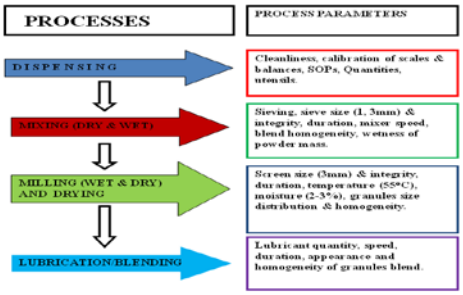

Fig. 1: Flow diagram showing processes and process parameters

The characteristic absorption bands of the actives did not shift significantly in the mixture even when the mixtures were wet kneaded, milled and dried at high temperature. Corroboration for this assertion could be found in **Figures 2-3 and Table 3**. The fact that the absorption bands of lumefantrine and artemether were identified by FTIR spectrometer in an 8-component physical mixture as contained in the figures and table meant that the actives as well as other components remained the same and unchanged. The similarity in spectral characteristics of pure materials, physical mixtures and granules bore testimonies to the compatibility of components of formulations on one hand and suitability of wet granulation as a process method on the other hand. Thus, the risks envisaged from materials incompatibility as well as those from unit operations within the process method especially wet kneading and drying at high temperature were adequately addressed by results from FTIR testing and screening. Wet granulation method has not negatively affected the quality of pure, starting as well as in-process materials as indicated in **Figure 3 and Table 3**. Using major spectral peaks to track and trace the compatibility and stability of formulation components and suitability of process method as shown in **Table 3** provided scientific justifications for the composition of the formulation and adoption of wet granulation method. Those major peaks were confirmed in starting, physical mixtures and in-process materials and hence a good account of process suitability. These results from FTIR testing seemed to be in conformity with observations of some drugs formulation researchers that have used FTIR spectrometer to confirm formulation components compatibility [7, 9]; process suitability [12] and both components compatibility and process suitability [8].

Table 1: **Mode of incorporation of AL into formulations**

Materials	**Composition of different Formulations**					
Stage 1: Wet granulation	**F – 1**	**F – 2**	**F – 3**	**F – 4**	**F – 5**	**F – 6**
Lumefantrine			✓	✓		✓
Artemether			✓		✓	✓
Microcrystalline cellulose	✓	✓	✓	✓	✓	✓
Maize starch	✓	✓	✓	✓	✓	✓
Sodium starch glycolate	✓	✓	✓	✓	✓	✓
Silicon dioxide	✓	✓	✓	✓	✓	✓
Polysorbate 80	✓	✓	✓	✓	✓	✓
Stage 2: Lubrication / Blending						
Lumefantrine		✓			✓	
Artemether		✓		✓		
Sodium starch glycolate (14%)	✓	✓	✓	✓	✓	✓
Magnesium stearate	✓	✓	✓	✓	✓	✓
Key: ✓ = Present,		L= Lumefantrine, A= Artemether,				

Table 2: Sampling plan for compatibility and method suitability study

Samples	**FT-IR**	**DSC**	**HPLC**
Artemether test sample (ATS)	✓	✓	✓
Lumefantrine test sample (LTS)	✓	✓	✓
AL binary physical mixture	✓	X	✓
Physical mixture of all excipients	✓	X	X
Physical mixture of all starting materials	✓	X	✓
Granules of formulations F-1 to F-6	✓	F-4, F-6	F-4, F-6
Artemether reference standard (RS)	X	X	✓
Lumefantrine RS	X	X	✓
KEY: X = Not performed	✓ = Performed		

Table 3: Summary of spectral bands (cm^{-1}) at different processing levels

Functional group	**Lumef-antrine**	**Arte-mether**	**AL mix**	**PM of all materials**	**F-4 granules**	**F-6 granules**
O-H, stretch	3760	3760	3754.28	3691.42	3760	3748.57
C–H, stretch	2943.8	2941.73	2942.94	3005.71	2940.37	2940.13
O=C=O, stretch	2377.14	2382.85	2377.14	2514.28	2377.14	2377.14
C=O, stretch	1632.36	1633.22	1635.67	1637.29	1633.77	2154.28
C–N, stretch	1259.47	1379.17	1260.53	1256.21	1254.36	1399.52
C–O, stretch	1084.44	1107.26	1085.95	1097.0	1077.81	1071
C–Cl, stretch	558.03	539.87	512.33	539.56	515.28	520

Key: A = Artemether, L = Lumefantrine, PM = Physical mixture

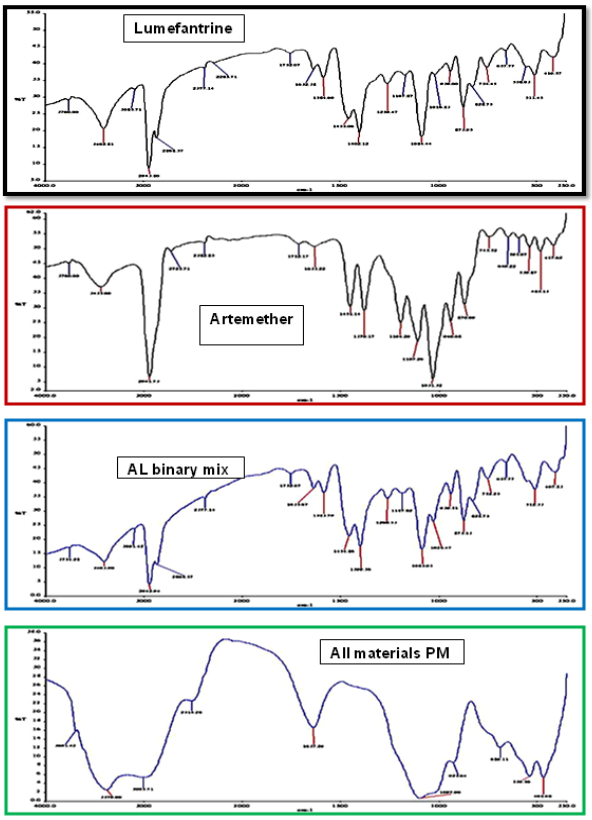

Fig. 2: FTIR spectra of artemether (A) and lumefantrine (L) in pure material and physical mixtures (PM)

DSC evaluation

The versatility of DSC as analytical tool to detect interaction and study thermal behaviours of materials were alluded to by results presented in **Figure 4** which showed thermograms at different stages of processing. Indeed, the DSC thermograms of artemether TS and lumefantrine TS as indicated in the figure showed that artemether has endotherm at peak maximum temperature of 89.7^{0}C which is within its corresponding melting point range of 86 – 90^{0}C as specified in official book [17], with its enthalpy of fusion represented by peak area given as -476.2 J/g. Another peak temperature indicated in the thermogram was at 176^{0}C which is probably due to any of the related substances of artemether and has peak area of 4622 J/g. On the other hand, lumefantrine thermogram as shown in the figure indicated only one peak maximum temperature at 133.4^{0}C which is not far from its melting point range of 128 – 132^{0}C. The enthalpy of fusion was given as -317.5 J/g. Matching thermograms across stages of processes indicated a decrease in peak maximum temperature from pure material to physical mixture and to granules. For example melting endotherm of artemether decreased from 89.7^{0}C in pure form to 87.7^{0}C in granules though marginally while peak temperature of lumefantrine reduced from 133.4^{0}C in pure form to 131.9^{0}C in granules of F-4. The reduction in peak temperature of both artemether and lumefantrine in F-6 was to the extent of 57.4^{0}C and 134.1^{0}C in granules respectively. In general, a decrease in peak maximum temperature and hence melting point of the materials in question, is an indication of a decrease in crystallinity of the materials as observed by other researchers and a tendency of the material to change to amorphous form if the reduction is substantial thus improving pharmaceutical properties of disintegration, solubility and dissolution [2, 9].

Chromatographic evaluation

Compatibility of AL with other formulation components was not only corroborated by chromatography but also indicated other related substances present in the formulations at different stages. By matching chromatograms developed from HPLC at various processing levels, it was evident that no significant interactions have occurred between drugs and excipients. With characteristic elution times of AL found in chromatograms of AL reference standard (RS), lumefantrine TS, artemether TS and binary mixture of AL TS, no significant shift in peaks elution times was observed when matching all the chromatograms thus confirming compatibility and stability of the actives. This similar elution times as formulations changed from physical mixtures to wet kneaded granules in both F-4 and F-6 could be regarded as evidence of process method suitability. The positions canvassed above were alluded to by the fact that only marginal shift occurred in elution times and varied from 2.96 min – 3.03 min (-0.9% to 1.1%) for lumefantrine and 5.65 min – 5.7 min (0.4% to 1.3%) for artemether when compared with elution time of mixed AL RS. This could be regarded as an indication of absence of important interactions that could have caused disappearance of old and appearance of new peaks at different elution times.

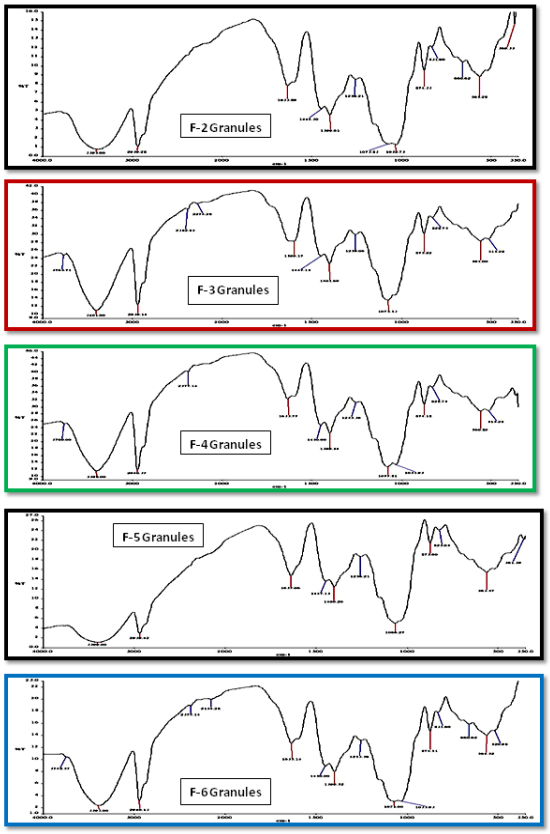

Fig. 3: FTIR spectra of artemether and lumefantrine in granules of different formulations

Potential risks evaluation

Outcome of an evaluation of risks that formulations were exposed to in the course of processing was presented in **Table 4** and showed important quality parameters that were considered and justifications for the classifications. Those quality attributes which variations may negatively impact the overall performance of the formulations were classified as critical quality attributes (CQAs) and these included all micromeritic properties. Critical components of processing technique at this stage were wet mixing and wet milling, drying and dry milling, all of which have greater impacts on granules sizes and size distribution hence bulk properties of granulates which includes flow rate and density, compressibility and homogeneity as also observed by other researchers [18]. This was the basis of classification of risks shown in **Table 4.** Other parameters that had

resulted from processing which may have impacts on flow properties include granules shape, moisture content and surface area, all of which have been linked to solubility and dissolution. As wet granulation was used as processing technique, the particles of starting materials were turned into granules of varying sizes and shapes; porosity and flowability, all of which had been modified to affect the physicochemical variables and the way the granules behave during subsequent processing. The observations of researchers were to the effects that bulk properties of granules such as flow, density, appearance, taste, color, texture, uniformity, segregation during mixing among others are contingent on particle size which in turn is affected by processing techniques [19, 20]. The lubricant (Magnesium stearate) added during lubrication / blending was critical as it reduced angle of repose and suppressed electrostatic effects on granules surface thus improving flowability.

CONCLUSION

The characteristic absorption bands of the AL did not shift significantly in the mixtures even when the mixtures were wet kneaded, milled and dried at high temperature to produce granulates. No disappearance of old and no appearance of new peaks observed in FTIR spectra at various processing stages. A decrease in melting endotherm of AL as shown by DSC thermograms as process progressed from physical mixtures to granules was an indication that crystal forms of the actives were being converted to partial amorphous form. Characteristic retention times of AL in the chromatograms at different levels of processing did affirm that no interaction would have occurred giving the similarity of the results. The assessment of potential risks informed the strategy deployed to monitor process and quality variables at various stages and allowed all known potential risks to be mitigated or controlled from the onset. However, further research work needs to be done to ascertain that artemether and lumefantrine remain in amorphous forms and do not re-crystallize any time throughout the life cycle of the resultant final product.

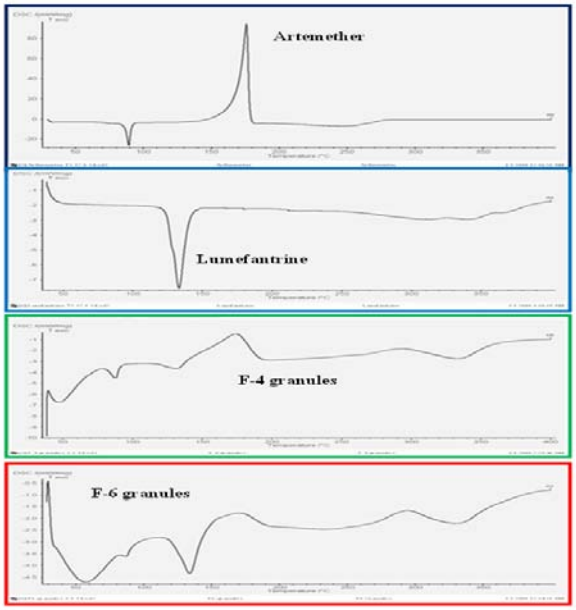

Fig. 4: DSC thermograms of artemether and lumefantrine at pure material and granules stages

Table 4: Classification of potential risks arising from process unit operations

Unit operations	Critical Quality Attributes of granules					
	Flow rate	Angle of repose	Bulk density	Tapped density	Hausner ratio	Carr's index
Dispensing	Low	Low	Low	Low	Low	Low
Dry mixing	Low	Low	Low	Low	Low	Low
Wet mixing	Medium	Medium	Medium	Medium	Medium	Medium
Wet milling	Medium	Medium	Medium	Medium	Medium	Medium
Drying	High	High	Medium	Medium	Medium	Medium
Dry milling	High	High	High	High	High	High
Lubrication/ Blending	High	High	Medium	Medium	Medium	Medium
Justification for risks classification	Sub-optimal wet mixing and milling may impact minimally on all flow parameters as proper granules may not have been formed under those circumstances. Both processes of drying and dry milling determine the moisture content, size, shape and size distribution of final granules and thus the bulk properties are affected by their outcomes. Proper lubrication and blending are germane for excellent micromeritic property of the granules. Milling (dry & wet) influences granules integrity, strength and size distribution, all of which may impact different levels of risks on flowability, compressibility, content uniformity and dissolution performance.					

CONFLICT OF INTERESTS

The authors declare no conflict of interests

ACKNOWLEDGEMENTS

The authors wish to place on records the support received from colleagues in the pharmaceutical industry. In particular, we thanked management and staff of Edo Pharmaceuticals limited, Benin City, Edo state, Nigeria where opportunity was given to use the facilities in the company including provision of materials.

REFERENCES

1. Narayankar S, Phadke M, Patil D, Jadhav RK, Ramesh S, Yamgar RS. Development of Discriminating Dissolution Procedure for Artemether and Lumefantrine Tablets. *Der Pharma Chemica* 2010; 2(6): 394-399.
2. 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. DOI 10.1007/s40005-013-0078-z
3. World Health Organization. Guidelines for the treatment of Malaria,1st edition. Geneva, WHO [Online], 2006; Available at: www.who.int/malaria/docs/TreatmentGuidelines 2006.pdf. (Accessed January 18, 2014)
4. World Health Organization. Guidelines for the treatment of Malaria, 2nd edition. Geneva, WHO press, pdf document, 2010; 1-210.
5. 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.
6. Bargal JS, Dhawale SC, Landage SN, Kulkarni RV. Formulation and evaluation of Eudragit RS 100 loaded Microsponges of Flutrimazole. *Int J Pharm Sci Res* 2013; 4(8): 3039-3045. doi: 10.13040/IJPSR. 0975-8232.4(8).3039-45
7. Gudikandula R, Madhavi K, Thakkalapally SR, Veeramalla A and Prasad IR. Enhancement of Solubility and Dissolution rate of

Ezetimibe through Liquisolid Technique. *Int J Pharm Sci Res* 2013; 4(8): 3229-3238. doi: 10.13040/IJPSR. 0975-8232.4(8).3229-38

8. Hosny KM, Khames A, Abd Elhady SS. Preparation and Evaluation of Orodispersible Tablets Containing Hydroxylbutyl-β-Cyclodextrin-Simvastatin Solid Dispersion. *Trop J Pharm Res* 2013; 12(4): 469 – 476.

9. Rahman Z, Zidan AS, Khan MA. Formulation and Evaluation of a Protein-loaded Solid Dispersions by Non-destructive Methods. *The AAPS Journal* 2010; 12(2): 158 – 170. DOI: 10.1208/s12248-009-9171-7

10. Maddela S, Maddi EG, Nadendla R. Immediate Release Formulation of Valsartan Capsule and Evaluation of its Compatibility by Non-thermal Methods. *American Journal of Advanced Drug Delivery* 2013; 1(3): 180-196

11. Otsuka M, MouriY, Matsuda Y. Chemometric Evaluation of Pharmaceutical Properties of Antipyrine Granules by Near-Infrared Spectroscopy. *AAPS PharmSciTech* 2003; 4 (3): Article 47, 1–7

12. Short SM, Cogdill RP, Anderson CA. Determination of Figures of Merit for Near-Infrared and Raman Spectrometry by Net Analyte Signal Analysis for a 4-Component Solid Dosage System. *AAPS PharmSciTech* 2007; 8(4): Article 96, 1–11

13. Mustapha MA, Igwilo CI, Silva BO. Effects of Wet Granulation Process Variables on the properties of Nifedipine Granules. *International Journal of Drug Formulation and Research* 2011; 2(5): 320–332

14. Mustapha MA, Igwilo CI, Silva BO. Influence of concentration of modified maize starch on compaction characteristics and mechanical properties of Paracetamol tablet formulation. *Medical Journal of Islamic World Academy of Sciences* 2013; 21(3): 125– 131

15. Hancock BC, Colvin JT, Mullarney MP, Zinchuk AV. The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets, *Pharm. Tech* 2003; 4: 64-80

16. 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.

17. The International Pharmacopoeia. 4th Edition. CD-ROM. Geneva, WHO Department of Essential Medicines and Pharmaceutical Policies, (2008)

18. Hellstrom J. A protocol for characterization of tablet manufacturability of drug and Pharmaceutical additives: [On line], 2005. Available at: www.farmfak.uu.se/farm /galfaf 2005. (Accessed June 15, 2010)

19. Dias VH, Pinto JF. Identification of the most relevant factors that affect and reflect the Quality of Granules by Application of canonical and cluster Analysis. *J. Pharm. Sci.* 2002; 19(1): 273–281

20. Mustapha MA. Formulation and process optimization of artemether-lumefantrine fixed dose combination tablets using Quality by Design approach. PhD Thesis, University of Benin: Benin City, December 2014.