Panacea Journal of Pharmacy and Pharmaceutical Sciences 2015:4(2);108-120

International Journal

PJPPS
Panacea Research Library
Journal Homepage: www.prlpublisher.com/pharmacy/pjpps

Panacea Journal of Pharmacy and Pharmaceutical Sciences
ISSN: 2349 7025

Original Research Article **Volume 04 Issue 02**

Quality by Design-based Formulation and Optimization of Artemether - Lumefantrine Fixed Dose Combination: Tablets evaluation

Musibau A. Mustapha*[1], Michael U. Uhumwangho, Magnus A. Iwuagwu

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City 300 001, Edo state, Nigeria

Article history:

Received: 27th April 2015

Received in revised form: **** May 2015

Accepted: **** May 2015

Available online: *****July 2015

Corresponding author:

Mustapha MA,

Email: musibaumustapha@yahoo.co.uk

Phone: +234 802 359 8499

***Present address*:**

Edo Pharmaceuticals Ltd; 44 First Federal road, Uselu, Benin City 300 001, Edo state, Nigeria

These authors have no conflict of interest to declare.

Abstract

Platform of quality by design (QbD) was explored to demonstrate within design space (DS) how inherent variations in materials and process were monitored and controlled to achieve robust process and quality product. This study was undertaken to evaluate tablets of Artemether - Lumefantrine (AL) fixed dose combination with a view to establish the fitness for purpose designed and built into the tablets. Tablets were compressed at predetermined compression force (40 MN/m^2) and qualities were profiled in line with predefined Quality Target Product Profile (QTPP) and DS. Analytical tools such as Fourier Transform Infra-Red (FTIR) and Differential scanning calorimetry (DSC) were engaged to elucidate what transpired during tablet processing; evaluation of potential risks to predefined QTPP and critical quality attributes (CQAs) was done and documented. Optimization process was concluded within DS and observed quality features demonstrated the criticality of process unit operations. Evidence from screening showed that inherent potential risks to tablets were properly curtailed to the extent that fairly good tablets from F-4 and F-6 were alluded to. FTIR spectral bands showed no disappearance of important old peaks and no appearance of new ones as DSC thermograms indicated no thermal disequilibrium but better pharmaceutical parameters arising from reduction in melting endotherm. It is opined that tableting as a process was robust and capable of delivering good performance on a reproducible basis given the observed quality attributes of the 2 formulations.

Keywords: Design space, quality, robustness, performance, processing, optimization

Introduction

Quality and drug formulation experts are of the opinion that QbD by its principles helps to identify critical materials attributes (CMAs), formulation variables as well as critical process parameters (CPPs) and determines the extent to which all of these will interact to bring variations that may affect the overall CQAs of the final products.[1,2]The information generated and data collected during QbD experiments on materials and process components, if properly analyzed and utilized will give insights into their impacts on quality, efficacy and safety and thus providing informed decision on the status of the finished product.[3,4]Hence, QbD is regarded as a systematic, scientific and modern approach that allows designing and building of quality into the product right from the onset. By its adoption, paradigm is shifted from traditional quality by testing and this enables better knowledge and understanding of critical variables of input, process and output.[5,6]This effort to formalize product design and development provides scientific understanding of compatibility of all input components and the process that drive the manufacture of the product. It also eliminates troubleshooting by trial-and-error. All quality related issues are brought forth, analyzed to identify root causes and subsequently resolved.[7,8]

The expectation from adoption of QbD is that manufacturers would demonstrate better knowledge and understanding of the process that drive the quality supposedly designed and built into their products;[9, 10] as QbD is thought to be a good business that helps companies to get to the market reliably fast. Characterization of pharmaceutical dosage forms especially tablets is of utmost importance as it enables formulation scientists to know to what extent the starting materials as well as in-process materials have responded to value-adding process. Assessment at different levels of processing using appropriate indices will show the utility in the in-process materials as well as final products and how well the requirements of specifications have been met. Comparison of information from such evaluation with innovators products as well as established indices could help to select other generic products for the purpose of interchange. Characterization brings forth new acquired properties of the products as being distinct from their inherent primary qualities as observed in previous research works.[11, 12]At tablets stage emphasis was on assessment of weight and content uniformity, tensile strength and porosity, disintegration time and dissolution, hardness and friability and assay as previously utilized by other researchers.[11-13]

In this research work, the approach of QbD was explored to evaluate tablets of AL fixed dose combination formulation specifically indicated for oral treatment of acute,

uncomplicated *Plasmodium falciparum* malaria in adults and children over 34kg as officially pre-qualified, approved and administered in line with Essential Medicines List of World Health Organization- WHO.[14]

Experimental

Preparation of tablets

Using manually operated single punch tablet press (Type F-3, Manesty, England), fitted with 12.5mm die, upper and lower punches which are round with flat face and brake score in upper punch, granules (as prepared in part one of this article) were compressed into tablets with compression force set roughly at 40 MNm^{-2} to give hardness of 4 to 8 Kp (40 – 80N). Resultants tablets were properly kept for further evaluations.

Tablets evaluation

During tablets compression, weight variation was monitored using Ohaus precision balance and only tablets within ±5% of formulation weight were selected for further assessment.After 24 hours of storage, the hardness (crushing strength) of the tablets was determined using digital Campbell Electronics hardness tester (Model HT- 30/50, Campbell Electronics, India). Diametral compression force of 10 tablets was singly determined, average 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 (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.

% Friability = (Wb – Wa) / Wb * 100 ------- 1

Disintegration time was evaluated with a disintegration apparatus (Manesty, England). One tablet each was put in each of the 6 tubes and hung on the apparatus to which container distilled water at temperature of 37 ± 1^{o}C has been added. The apparatus was switched on and the time it took each tablet to completely break down into particles smaller enough to pass through predetermined aperture of the mesh was determined. Average and standard deviation were also estimated.

Optimization process

Steps were taken to optimize formulations and processeswith a view to choose those that will deliver expected qualities on a consistent basis.

Evaluation of stickiness of formulations

The sticking propensity of each formulation was assessed by compressing a fixed number of tablets and the amount of granules that got stuck to the walls and tip of die and punches carefully scraped, removed and weighed. The quantity is expressed as a percentage of tablets compressed.

Risks assessment of CQAs of tablets

QTPP for the finished tablets were predefined using official reference books [15, 16] and prior knowledge as indicated in Table 1.Quality parameters which variations may negatively impact the overall performance of the tablets were classified as CQAs and the risks associated with them due to processing were assessed for impacts. Samples of tablets from formulations F-1 to F-6 were taken and evaluated for stability to provide for early detection and prevention/ mitigation of risks at development stage.

Stability study

Intermediate stability study as recommended by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH Q1A (R2) [17] and World Health Organization [18]was carried out by keeping the tablets at intermediate storage conditions of between 28 - 32ºCtemperature and relative humidity of 60 – 70% over a period of 60 days. The tablets were packaged in impermeable aluminum foil and samples taken and tested for stability using FTIR and DSC as previously outlined.[19] Spectra and thermograms were collated, analyzed and matched at different sampling time to detect significant differences that may indicate instability and hence product deterioration.

Results

QTPP that predefined the characteristics of the expected tablets and the justification for classifying some of them as CQAs was contained in Table 1 while Table 2 showed the outcome of risks assessment of effects impacted on each of the CQAs by the unit operations. The effects were found to range from low to medium and to high in different cases. Table 3 showcased the observed quality attributes of formulations processed in different ways. These quality parameters were monitored during tablets compression; and in Table 4 were the results of optimization process and its effects on pharmaceutical parameters. FTIR spectra as contained in Figure 1 and DSC thermograms in Figure 2 indicated no shift in absorption bands and thermal properties.

Discussion

The drug design objective which is made up of quality attributes of the tablets were derived from monographs in official books.[15, 16] Those properties which variations may impact the quality, efficacy, safety and hence the performance of final product were classified as CQAs and were shown in Table 1 and constituted the quality targets of the tablets in focus.

Table 1: Predefined Quality Target Product Profile (QTPP) and Critical Quality Attributes

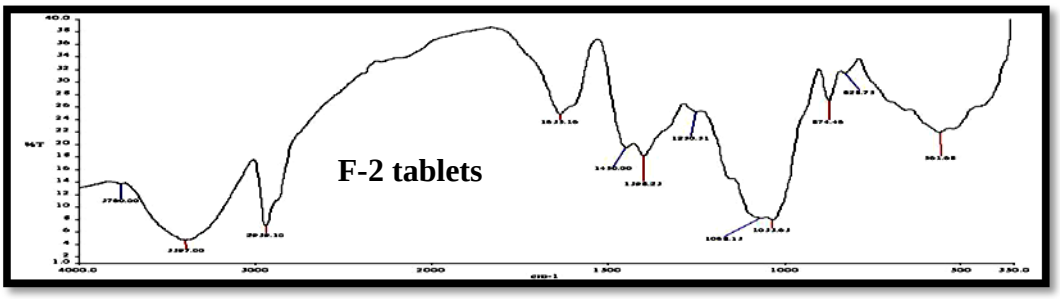
Quality Attributes	**Targets**	**Justification**
Dosage form and strength	Oral tablets with 240/40mg of LA per tablet.	By taking 2 tablets twice daily for 3 consecutive days, the requirement of 6 doses in 3 consecutive days by WHO will easily be met. Some approved brands followed same. Accuracy of dosage strength is a CQA in line with compendia specifications.
Appearance	Yellow, smooth, round tablets. No cracking and sticking.	Aesthetics is important though not a CQA for patient appeal and compliance. Excessive cracking, picking and sticking make tablets look rough and less enticing.
Weight uniformity	Formulation weight ±5%	Compendia specification for tablets of this weight is ±5%. Besides, accurate content uniformity of actives is contingent on accurate weight of the tablets. Thus uniformity of tablet weight is a CQA.
Hardness (Crushing force)	4 – 8Kp (40-80N)	Besides its ability to keep tablet intact throughout its lifecycle, hardness plays key roles in friability, disintegration and dissolution of tablets. It is therefore a CQA.
Friability	Less than 1%	Protection of tablets breakages from normal and abnormal stresses during processing and transportation informed this compendia limit.
Disintegration time	Less than 15 min	This is a CQA as other parameters such as dissolution and drug release are contingent on it. It is equally a compendia requirement that uncoated tablets must meet.

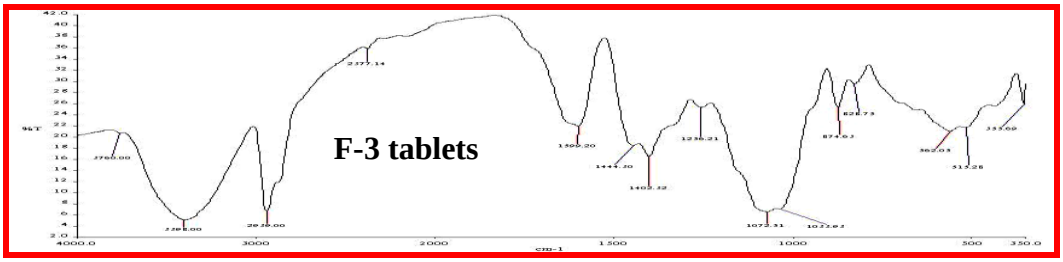
Table 2: Assessment of potential risks to CQAs due to Processing

Unit operations	**Critical Quality Attributes (CQAs) of finished tablets**					
	Weight uniformity	**Hardness**	**Friability**	**DT**	**Dissolution**	**Assay**
Dispensing	Low	Low	Low	Low	Low	Medium
Dry mixing **Wet mixing**	Low Low	Low Medium	Low Medium	Low Low	Low Medium	High Low
Wet milling **Drying** **Dry milling**	Low Low Medium	Medium Medium Medium	Low Medium Low	Low Medium Medium	Low Low Medium	Low High Medium
Lubrication / Blending	High	Medium	Medium	High	High	Low
Tablet compression	High	High	High	High	High	High
Justification for risks classification	Suboptimal mixing (dry & wet) may impact risks on hardness and friability, dissolution and assay (content uniformity). 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. Hence intensive monitoring is required. Improper drying may cause degradation of actives hence higher risk impact on assay. Lubrication and blending are key and pose high risks to those CQAs as shown above. The effects are minimal on assay. A lot of variables involved in compression such as granules flow, segregation, speed of tablet press and feeder frame, turret speed, hopper and compression force may impact high risks on all CQAs as listed. The process requires proper monitoring to reduce risk impacts. The operating design space was based on the limits set out in official reference books and prior knowledge of processes involved in wet granulation methods.[11-13] The limits were set to accommodate inherent variability in CPPs and CQAs and were verified during processing as evidenced in Table 3.					

Table 3: Summary of observed pharmaceutical properties of tablets of formulations

Properties	**F – 1**	**F – 2**	**F – 3**	**F – 4**	**F – 5**	**F – 6**
Mean weight (g, n=10, ±SD, %RSD)	0.5495 ±0.0142 2.58	0.5507 ±0.0143 2.61	0.5527 ±0.015 2.72	0.5581 ±0.0083 1.48	0.5527 ±0.0115 2.09	0.5521 ±0.0084 1.52
Mean hardness (Kp, n=10, ±SD)	4.72 ±1.07	4.37 ±0.556	3.99 ±0.398	6.15 ±1.132	6.9 ±0.994	4.8 ±0.422
Mean DT (s, n=6, ±SD)	73.67 ±16.256	25.83 ±3.312	1072.67 ±34.697	124.5 ±12.145	16.17 ±8.40	75.33 ±23.517
Mean friability (%, n=3, ±SD)	2.3 ±0.30	0.52 ±0.08	0.20 ±0.02	0.2067 ±0.012	0.3967 ±0.025	0.2433 ±0.059
Hardness/friability ratio (HFR)	2.052	8.404	19.95	29.753	17.393	19.729
Remarks	The formulations' granules were observed to have propensity for stickiness to the walls of die and punches. This was however fair in F-4 and F-6 respectively					





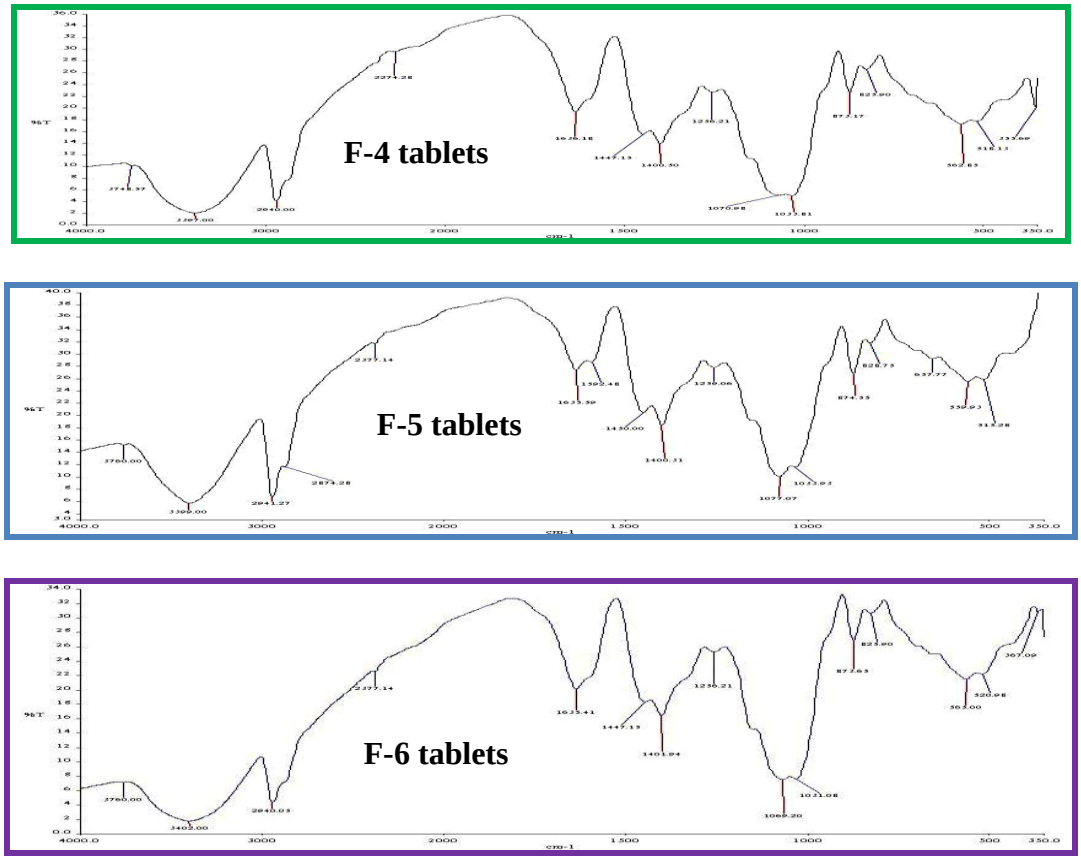


Figure 1: FTIR spectra of tablets of various formulations

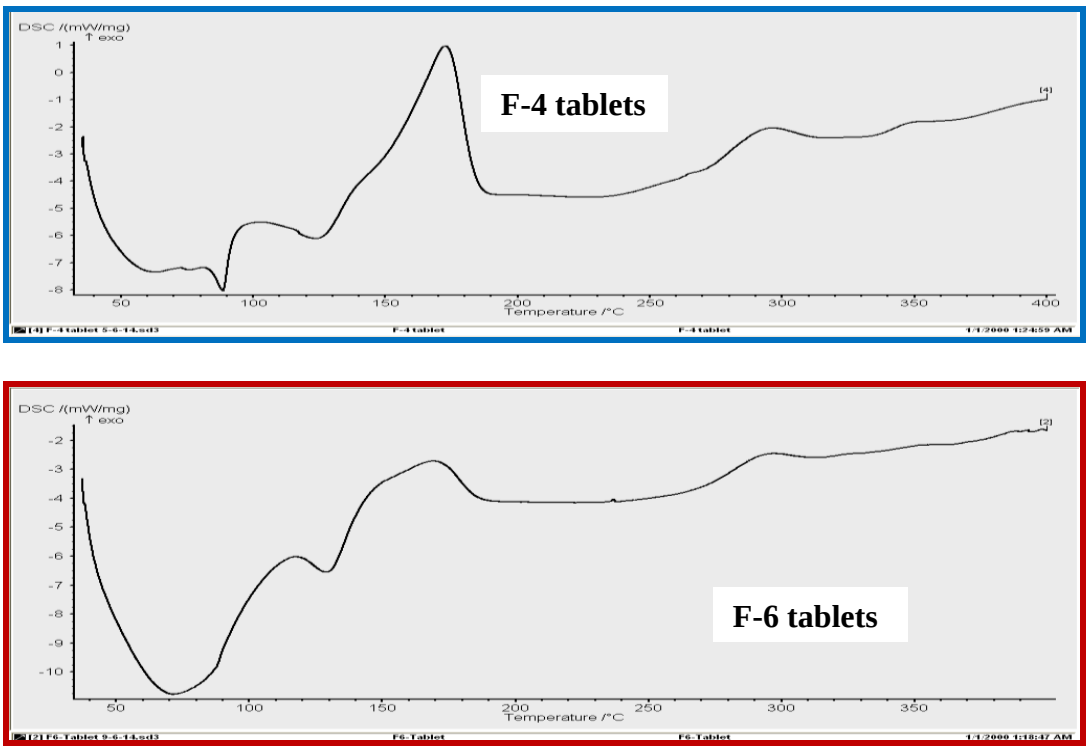


Figure 2: DSC thermograms of AL in tablets of different formulations

Risks assessments

Evaluation of FTIR spectra as contained in Figure 1 and DSC thermograms in Figure 2 developed after 60 days of stability studies revealed no important shift in absorption bands and no thermal instability as process progressed finally to tablet compression. This has shown that all processes including tablet compression has not significantly caused disappearance of old peaks and appearance of new ones. Matching DSC thermograms of AL in tablets of F-4 and F-6 indicated a marginal decrease in peak maximum temperature of both actives. For example, melting endotherm of artemether decreased from 89.7^{0}C in pure form to 88.8^{0}C in tablets while peak temperature of lumefantrine reduced from 133.4^{0}C in pure form to 123.7^{0}C in tablets of F-4 respectively. The reduction in peak temperature of both artemether and lumefantrine in F-6 was moderate as it changed to 71.5^{0}C and 129.1^{0}C in tablets respectively. Researchers have noted that a decrease in melting endotherm of materials is a sign of a decrease in crystallinity of the materials and a tendency of the material to be partially amorphous. This makes for better quality parameters of solubility, disintegration and dissolution of the final tablets.[20, 21]

Further assessment of risks that CQAs were exposed to in the course of processing was done as presented in Table 2. Important quality parameters as listed in the table were considered in line with unit operations they encountered. Justifications for the classifications were provided as enumerated in the table. As a requirement of QbD, the outcome of the assessment informed the strategy deployed to monitor process and quality variables at various testing stages to determine parameters such as tablets weight uniformity and hardness, friability and disintegration, dissolution among others. This allowed all known potential risks to be mitigated or controlled from the outset.

Pharmaceutical characteristics of tablets of various formulations

The results of characterization of tablets from formulations F-1 to F-6 using dependent variables of weight uniformity and hardness, friability and disintegration were chronicled in Table 3. In particular, the tablets weight varied marginally across formulations and with relative standard deviation (RSD) of ≤ 2.72%, it could be confirmed that weight variation was minimal and within official specification of less than 5% thus alluding to proper monitoring of tablets weight as a CQA. Hardness is another CQA that is subjected to vagaries of tableting process. With values across formulations as shown in Table3, it was opined that the tablets are strong enough to withstand both normal and abnormal stresses during handling. Except in F-1 which is a placebo and has high friability of 2.3±0.3, the strength of hardness was reflected in the level of friability exhibited by other formulations as depicted in Table 3. All showed values which were lower than 1%

maximum official specification. With hardness /friability ratio of 2.05 to 29.75, it could be concluded that the tablets are strong enough to remain intact as posited by other researchers.[11,22] In-spite of high hardness/friability ratio which is a good evidence of mechanical strength, results of evaluation of DT shown in Table 3 with exception of F-3, did not show adverse effects on disintegration. DT across formulations was an evidence of timely disintegration of tablets.

Table 4: Outcomes of optimization process

Quality parameters	**Formulations**	**Lubricant (Mg stearate) concentrations (%)**				
		0.4	**0.6**	**0.8**	**1.0**	**1.2**
Hardness (Kp)	F-4	7.33	7.41	6.89	7.63	7.49
	F-6	5.84	5.14	5.72	6.51	5.72
Disintegration time (s)	F-4	53.83	44	50	52	45.5
	F-6	78.67	67.5	72.5	61.5	57.5
Friability (%)	F-4	0.299	0.38	0.569	0.282	0.188
	F-6	0.403	0.188	0.372	0.185	0.372
Hardness – friability ratio (HFR)	F-4	24.51	19.5	12.11	27.06	39.84
	F-6	14.49	27.34	15.38	35.19	15.38

Consequences of optimization process

Physical observations during tablets compression were to the effects that all formulations but to a lesser extent F-4 and F-6 had high level of fine powder after granulation and a propensity for stickiness. This was probably responsible for rough appearance of tablets which was slightly better in F4 and F6. It was also probable that lumefantrine was culpable in this problem of stickiness which was evident when tips and walls of punches and die were examined after each formulation compression that lasted for about 20 min. For this reason, optimization was done to reduce stickiness and improve tablets esthetics as recommended by other researchers.[23]

Ppharmaceutical properties of harness, friability and DT were not affected by the optimization process even when the quantities of lubricant were increased from average of 0.4% to 1.2% as showed in Table 4. This culminated in improved quality of tablet appearance.

Conclusion

In summary, specifications of CQAs as contained in reference books including mass uniformity and tablets hardness, friability and DT were met by F-4 and F-6 and will be compared in a later research work with a standard commercially manufactured product of the same strength of 40/240 mg AL. Optimization of processes and formulations were done and better results achieved within DS and did not affect quality targets. With proper monitoring of variables involved in tablets compression, all high risks impacts on CQAs were controlled as shown by observed pharmaceutical qualities of F-4 and F-6. It stands to reason therefore that the process utilizedin F-4 and F-6 was optimal and capable of delivering good product performance. The study revealed hidden knowledge and understanding required to guarantee robust process control and assurance of quality ofAL in a fixed dose combination product on a constant basis.

Competing interest

The authors declare that they have no competing interest.

Acknowledgments

The authors acknowledged and therefore grateful to management of Edo Pharmaceuticals Limited, Benin City for provision of materials and other equipment used in this research work.

References

1. Weichbrodt N, Camalo M. Using Quality by Design to Optimize Tech Transfer of Advanced Sterile Processing. Pharmaceutical Manufacturing Special report 2012; 3-7.
2. Ukeje AM. Predevelopment activities hold the key to successful Drug manufacturing. Pharmaceutical Manufacturing Special report 2012;8-16.
3. Polywacz A. Holistic QbD. Pharmaceutical Manufacturing 2011; 1-5. Available at: www.pharmamanufacturing.com/articles/2011/068.html?_page=full.Cited 23/9/13.
4. Winkle HN.Implementing QbD. Food and Drug Administration 2007. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices /CDER/ucm103453.pdf. Cited 23/09/13.
5. Hlobik T. Developing a QbD component: The lifecycle of Syringe Plunger. Pharmaceutical Manufacturing2011;6-8.Available at:www.pharmamanufacturing.com/articles/2011/068.html?_page=full.Cited 15/10/13.

6. Thomas P. QbD for Pharma Packaging components: A solution Provider gets more science-based. Pharmaceutical Manufacturing 2011;9-11.Available at:www.pharmamanufacturing.com/articles/2011/068.html?_page=full.Cited 15/10/13.
7. Markarian J. Defining Design Space in Hot-Melt Extrusion. Equipment and Processing Report. Pharmaceutical TechnologyJuly 2012. Available at: http://www.pharmtech.com/pharmtech/author/authorInfo.jsp?id=59646.Cited 15/10/13.
8. DPT Thought Leadership. What Is Quality By Design (QbD) – And Why Should You Care? DPT labs 2013; Issue 11: No.1. Available at: www.DPTLABS.com.Cited 15/10/13.\
9. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH – Q8 (R2), Pharmaceutical Development 2009; Geneva, ICH.
10. Nasr MM. Implementation of Quality by Design (QbD) – Current Perspectives on opportunities and challenges. Food and Drug Administration 2011; 1-33. Available at: www.fda.gov/downloads/AboutFDA/CentersOffice/CDER/.Cited 11/11/13.
11. Mustapha MA, Aluya QA, Ihunde JE.Formulation development and quality profiling of Paracetamol – Ibuprofen combination tablets.Int J Pharm Sci Res 2014; 5:964-969.doi: 10.13040/IJPSR. 0975-8232.5(3).964-69.
12. Bravo SA, Lamas MC, Solomon CJ.In vitro studies of diclofenac sodium controlled – release from polymeric hydrophilic matrices. J PharmSci2002;5:213–219.
13. Mustapha MA, Igwilo CI, Silva BO. Quantifying the Influence of Wet Granulation Process Variables on the Properties and In Vitro Dissolution of Oral Controlled Release Nifedipine Tablets. Asian Journal of Pharmaceutical Sciences and Research 2011; 1:19–28.
14. World Health Organization. Guidelines for the treatment of Malaria,1st edition. Geneva, WHO.Available at: www.who.int/malaria/docs/ Treatment Guidelines 2006.pdf. Cited 13/4.14.
15. The International Pharmacopoeia, 2008; 4th Edition. CD-ROM. Geneva, WHO Department of Essential Medicines and Pharmaceutical Policies, 2008.
16. British Pharmacopoeia, 2008. CD – ROM; Version 12. London, The Stationery Office, 2008.
17. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. Stability testing guidelines; Stability Testing of New Drug Substances

and Products (ICH Q1A (R2)), 2003. Geneva. ICH

18. World Health Organization. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, Annex 2. WHO Technical Report Series, No. 953, 2009.
19. Mustapha MA, Iwuagwu MA, Uhumwangho MU. Compatibility and processing methods study of formulation of artemether–lumefantrine fixed dose combination using analytical tools. Innovare Journal of Science 2015; 3(2): 8-13.
20. 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.
21. Rahman Z, Zidan AS, Khan MA.Formulation and Evaluation of Protein-loaded Solid Dispersions by Non-destructive Methods. The AAPS Journal 2010; 12: 158–170. DOI: 10.1208/s12248-009-9171-7
22. 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. Available at: www.pharmtech.com.Cited 12/12/13.
23. Mullarney MP, MacDonald BC, Hutchins A.Assessing Tablet-Sticking Propensity. Pharmaceutical Technology 2012; 36:57-62.

    Available at: http://www.pharmtech.com/pharmtech/author/authorInfo.jsp?id=56803.Cited 12/12/13.