Panacea Journal of Pharmacy and Pharmaceutical Sciences 2015:4(2);121-131

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 4 Issue 2**

Quality by Design-based Formulation and Optimization of Artemether - Lumefantrine Fixed Dose Combination I: Granulates assessment

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Article history:

Received: 27th April 2015

Received in revised form: 10th May 2015

Accepted: **** May 2015

Available online: *****July 2015

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These authors have no conflict of interest to declare.

Abstract

This study was carried out to assess granulates of Artemether - Lumefantrine (AL) fixed dose combination so as to throw more light on the effects of processing techniques, usefulness of formulations and process method as envisaged from adoption of principles of quality by design (QbD). Wet granulation method was adopted; both formulation and process optimization were done and achieved within design space (DS); and the resultant granules were characterized for micromeritic properties and optimized to give quality granulates that were useable in next processing stage. Characterization indices of flow rate, angle of repose, bulk and tap densities, Hausner ratio and Carr's index were used to establish the bulk properties of the granulates. Evaluation of potential risks to predefined parameters and critical quality attributes (CQAs) was done and documented. Indications from observed quality indices elucidated the critical nature of order of addition of AL during processing. Intrinsic potential risks were controlled to the extent that fairly good granulates were produced with flow rate of ≥ 0.45 g/s, angle of repose of ≤ 37.67º, bulk density of ≥ 0.48 g/ml, tapped density of ≥ 0.54 g/ml, Hausner ratio of ≤ 1.265 and Carr's index of ≥ 11.68%. Stability study confirmed no substantial changes in the granules that could cause instability in future when stored for 60 days at intermediate storage conditions of 30 ±2ºC temperature and 65 ±5% relative humidity. It is considered that the process and mode of incorporation of AL into formulations F-4 and F-6 during wet massing were capable of consistent performance as illustrated by the achieved quality parameters of the granules.

Keywords: Characterization, index, risk, parameter, granulation, density

Introduction

According to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH – Q8 (R2)), QbD is a systematic approach to pharmaceutical ters that have been demonstrated to provide assurance of quality.[1] In principle, QbD comprises of components namely product and process, control and operating design spaces, the bases of which are rooted in science and risk management.[3] Although process performance is hinged on proper identification and control of critical process variable parameters, products including pharmaceutical dosage forms are expected to be designed with qualities that meet the requirements of end users; and this will require formulation and processing that deliver desired quality, efficacy and safety. For these reasons, quality experts opined that adoption of QbD ensures robust laboratory and commercial process and its optimization.[4] Its adoption also ensures proactive approach to product development, processing and manufacture that help to enhance regulatory compliance; [2] collection of scientific data that assist in identifying root cause and resolution of deviations, better understanding of risks associated with inputs, process and finished products that allows mitigation and contingency plans to address risks throughout product lifecycle.[5] Guided by these assertions, adoption of QbD provides knowledge about limits and risks associated with formulation and production methods thus preventing rejects, reworks, reprocess and loss. It maximizes process efficiencies and product performance throughout the life cycle of the products. [6, 7]

Formulation experts of various schools of thought have recommended some physical, physicomechanical and physicochemical indices to be engaged during characterization which at granules level include features such as bulk and tapped densities, angle of repose and flow rate, Carr's index and Hausner ratio. All these show how the primary materials have undergone wet granulation processing to become in-process granules that are different from initial entities and also show how the granules will perform in the next stage of processing.[8-10] The emphasis in this study was on optimization and sequence of addition of AL during processing with a view to deliver product with efficient performance.

Experimental

Formulation design space (DS):

Granules were made of 43.62% Lumefantrine and 7.27% Artemether (Vital Healthcare, India), 4.18% Maize starch (Royal Ingredients, Holland), 21.82% Microcrystalline cellulose (J. Rotten Maier and Sohnne, Germany), 0.91% Silicon dioxide (Evonik Degussa, Germany), 20% Sodium starch glycolate (Rosswell, India), 1.82% Polysorbate 80 (Irish Country Gold, Ireland), and 0.38% Magnesium stearate (S Kant Healthcare, India). All these pharmaceutical grade materials were gifts from Edo

Pharmaceuticals Ltd, Benin City, Nigeria and used as such as previously reported.[11]

Preparation of granules

Each component in the design space was accurately weighed using Ohaus Precision standard balance (Ohaus Corporation, USA) and manually pressed through sieve size 1mm to remove lumps. Respective components were added to the mixing machine (Hobart, England) and dry-mixed for 3 min. Polysorbate 80 was mixed manually in 200 ml demineralised (DM) water, the mixture added to the powder blend in the mixer and kneaded for 6 min to achieve homogenous wet mass which was manually sieved using 3 mm mesh. 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% as analyzed using Ohaus moisture analyzer (Ohaus, China). Dried granules were manually pressed through 3 mm sieve to get free flowing particles and together with other additives and lubricant were poured into the mixer and blended for 3 min. Mode of incorporation of AL into respective 6 formulations coded F-1 to F-6 was as detailed in Table 1.

Characterization of granules

Flow rate and angle of repose

Funnel method of determining flow rate and angle of repose was adopted as previously used.[9] However, the funnel has a base diameter of 88 mm, efflux length of 55 mm and orifice diameter of 4 mm. The time it took 20 g of granules to flow out through the funnel efflux length with gentle tapping was noted while the funnel was fixed at height of 66 mm from the base floor. The granules were allowed to flow onto a sheet of paper where they formed cones. The diameters and the height of the cones were measured and the radii estimated from the diameters. The angle of repose (θ^{o}) was calculated using equation 1.

θ^{0} = Height ÷ Radius * $\tan^{-1}$ ---------- 1

Measurements were in triplicate; and mean and standard deviation calculated.

Bulk and tapped densities

30 g of granules was weighed and carefully added into a graduated measuring cylinder in a slant position. The cylinder was gently put upright and the bulk volume occupied by the granules was noted. The tapped density was evaluated by tapping the cylinder containing the granules 100 times on hard surface from height of 50 mm. The volume was thereafter noted. The measurements were made three times and mean and standard deviation estimated. Both bulk and tapped densities were extrapolated using the equations 2-3.

Bulk density = Weight of granules (g) ÷ Bulk volume (ml) ---------- 2

Tapped density = Weight of tapped granules (g) ÷ Tapped volume (ml) ---------- 3

Hausner ratio and Carr's index

Estimation of Hausner ratio and Carr's index (compressibility index) was done using the data

obtained from measurements of densities. The under listed equations 4 & 5 were applied namely:

Hausner ratio = Tapped density ÷ Bulk density- 4

Carr's index (%) = Tapped density − Bulk density ÷Tapped density *100 ---------- 5

Optimization process

Rearrangement of excipients

Arising from observations during processing of formulations F-1 to F-6, it was evident that formulations F-4 and F-6 were the best even though some level of stickiness of granules to the wall of die and upper punch was seen in these formulations as well. Process optimization was carried out by rearrangement of excipients used in wet granulation and blending / lubrication stages respectively. Quantity of excipients in the external stage was increased from average of 3.16% to 7.42% in F-4 and 5.6% in F-6. However, the rearrangement did not affect the overall quantity as anticipated in the formulation DS.

Lubricant optimization

Taking cognizance of level of stickiness noticed during process optimization, the quantity of magnesium stearate used as lubricant was increased sequentially from 0.364 to 1.2%, (i.e. formulation optimization). The range was 0.4, 0.6, 0.8, 1.0, 1.2% respectively and was applied in F-4 and F-6 only and not to other formulations F-2, F-3 and F-5 due to high level of stickiness observed in them.

Intermediate stability study of granulates

Stability of granules and AL contained therein that may be affected adversely by processing such as dry and wet mixing, drying and dry milling, lubrication and blending; and hence impacted the overall performance of the output was evaluated during stability studies as espoused by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH Q1A (R2)) and World Health Organization.[12, 13] Granules packaged in impervious aluminum foil were kept at intermediate storage conditions of temperature range of 30 ±2ºC and relative humidity of 65 ±5%. Samples of granulates from formulations F-4 and F-6 were taken at 60 days and evaluated for stability using FTIR and DSC instruments as previously itemized. [11] Spectra and thermograms were collated and compared. This helped to detect, prevent and or mitigate risks at early stage of product development.

Results

The sequence of addition of AL into various formulations was as indicated in Table 1 while Table 2 contained the outcomes of optimization processes some of which include reduced stickiness. The micromeritic properties of granulates which showcased the bulk flow parameters before optimization were chronicled in Table 3 for all formulations as Table 4 showed the improvements in flow properties after optimization. FTIR spectra in Figure 1 and DSC thermograms in Figure 2 alluded to stability of

optimized formulations F-4 and F-6 at 60 days of storage.

Table 1: Mode of incorporation of AL into different formulations

Formulations	Process and other modifications carried out on formulations
F – 1	F-1 has no lumefantrine and artemether (LA) incorporated and was thus a placebo to demonstrate the utility and effectiveness of the matrix composition.
F – 2	In F-2, LA was extragranularly incorporated during blending similar to direct compression method using placebo granules produced in F-1.
F – 3	LA was jointly incorporated intragranularly during wet granulation.
F – 4	Lumefantrine was wet granulated internally while artemether was added extragranularly during blending in.
F – 5	In F-5, Artemether was incorporated intragranularly during wet massing while lumefantrine was added externally during blending.
F – 6	In F-6, the total quantity of excipients was divided into two and each was used to granulate artemether separately and lumefantrine separately. The mixtures were combined after drying; and lubricant added and blended.

Table 2: Consequences of optimization on formulations

Propensity of formulations for stickiness expressed as % of granules estimated.	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Values (%) before optimization	N/A	0.31	0.25	0.18	0.31	0.15
Values (%) after optimization	N/A	N/A	N/A	0.06	N/A	0.03

Key: N/A = Not applicable.

Table 3: Micromeritic properties of granules of formulations before optimization

Parameters	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Flow rate (g/s, n=3, ±SD)	1.115 0.088	0.170 0.023	1.397 0.044	1.125 0.031	0.450 0.039	0.80 0.019
Angle of repose (θ^o, n=3, ±SD)	31.64 0.82	34.71 0.90	34.44 0.26	31.42 2.21	35.89 4.21	37.67 0.72
Bulk density (g/ml, n=3, ±SD)	0.516 0.007	0.544 0.004	0.548 0.009	0.483 0.006	0.516 0.007	0.544 0.004
Tapped density (g/ml, n=3, ±SD)	0.689 0.001	0.542 0.007	0.620 0.012	0.560 0.008	0.653 0.011	0.672 0.006
Hausner ratio (n=3, ±SD)	1.148 0.034	1.248 0.025	1.133 0.035	1.161 0.032	1.265 0.038	1.234 0.018
Carr's index (%, n=3, ±SD)	12.87 2.59	19.85 1.63	11.68 2.73	13.84 2.4	20.91 2.41	18.95 1.18

Table 4: Summary of micromeritic parameters of optimized F-4 and F-6

Parameters	**F-4**	**F-6**
Flow rate (g/s, n=3, ±SD)	0.703 ± 0.060	0.725 ± 0.020
Angle of repose (θ^o, n=3, ±SD)	30.32 ± 0.61	29.12 ± 1.11
Bulk density (g/ml, n=3, ±SD)	0.487 ± 0.002	0.492 ± 0.003
Tapped density (g/ml, n=3, ±SD)	0.537 ± 0.030	0.554 ± 0.003
Hausner ratio (n=3, ±SD)	1.10 ± 0.06	1.13 ± 0.01
Carr's index (%, n=3, ±SD)	9.09 ± 5.46	11.25 ± 1.08

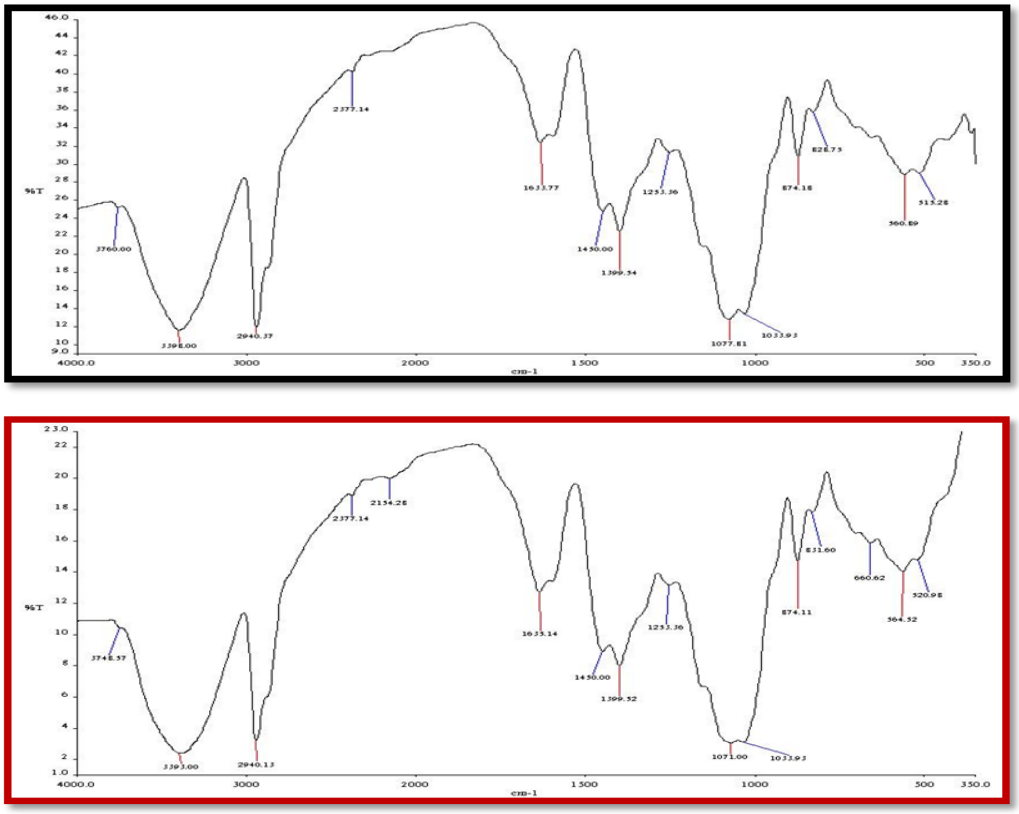

Figure 1: FTIR spectra of granules of optimized F-4 and F-6 at 60 days of storage in intermediate conditions

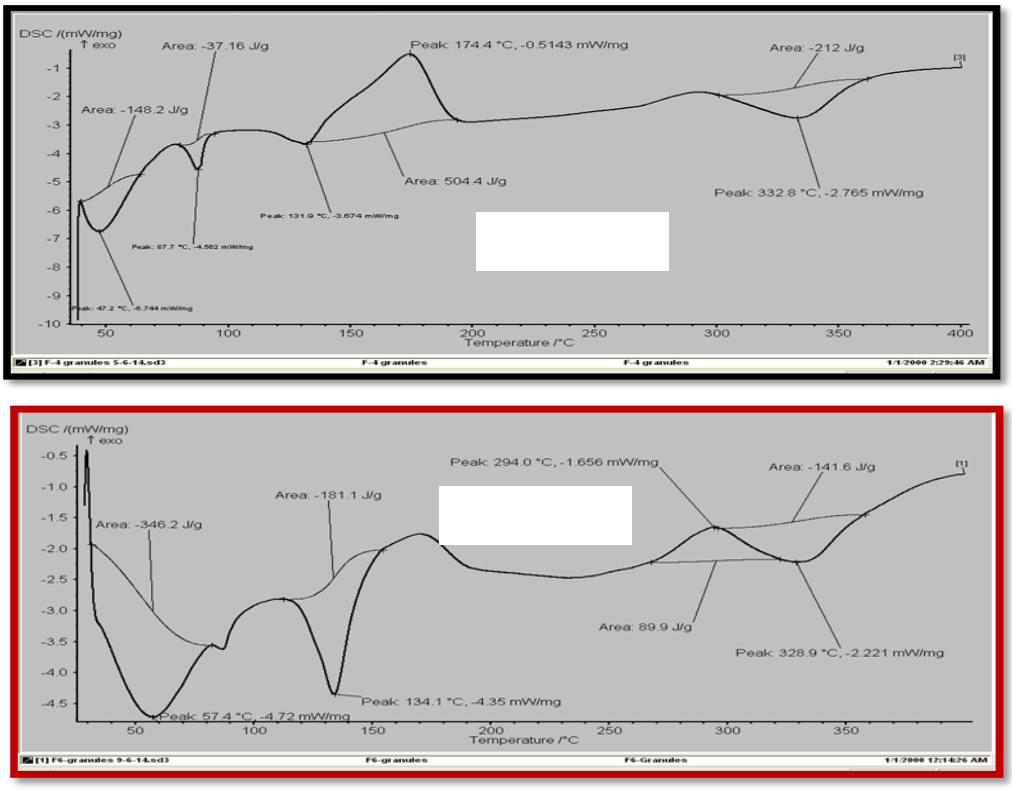

Figure 2: DSC thermograms of granules of optimized F-4 and F-6 at 60 days of storage in intermediate conditions

Discussion

As previously reported, the compatibility of formulation components and suitability of wet granulation as a processing method were not in doubt.[11] This provoked further evaluation of other properties of the formulations as encapsulated in this study. An assessment of each of the critical material attributes (CMAs) of the formulation showed that all the materials are not free flowing hence the need to adopt wet granulation method to produce granules of better flowability. The inherent insolubility and impermeability of both lumefantrine and artemether informed the composition of the formulations. For example, inclusion of polysorbate 80 improved solubility while silicon dioxide reduced the stickiness of lumefantrine among other utilities of components.[14]

Although the composition of all formulations is similar thus making the effects of formulation variables inconsequential, the process which each formulation went through was however different. As a consequence of order of addition of AL into formulations, F-1 has no AL incorporated and was thus a placebo that demonstrated that the matrix composition was no hindrance to attainment of predefined quality features as shown by its characteristics. Where AL was extragranularly incorporated akin to direct compression method using placebo granules, the level of fine powder was high due probably to the effect of AL load (about 50.89%), all of which is in powdery form. This was the situation with F-2 and the level of fine powders remained unacceptable as it affected smooth granules compression by causing high level of stickiness to the wall of punches and die and poor flow indices. Specifically, F-3 differs from F-6 on account of order of addition of AL. Whereas AL was jointly incorporated internally in F-3, they were individually added in F-6. This was done by dividing the excipients into two halves and each half used to wet granulate each of lumefantrine and artemether separately. The 2 mixtures were then blended together with other excipients to get granulates. The process adopted in F-6 gave better results as shown in Tables 2 - 4. Formulations F-4 and F-5 are similar in processing except that AL was interchanged. Whereas artemether was added extragranularly during blending in F-4, it was incorporated intragranularly during wet massing in F-5 and vice versa for lumefantrine. Juxtaposing outcomes of previous study [11] with this current one, it was logical to assert that no significant changes in quality parameters giving the results from preformulation and formulation evaluations even after storage of the in-process materials at intermediate storage conditions of temperature and relative humidity for a period of 60 days.

Risks assessments through stability studies

Evaluation of FTIR spectra of AL in granules of optimized formulations F-4 and F-6 at 60 days of storage and compared with spectra of pure AL previously reported,[11] revealed no important

shift in absorption bands during stability study as depicted in Figure 1. These assertions were supported by spectral bands identified in the formulations which included **O – H** at wave number (cm^{-1}) of 3748.57 (F-4), 3760 (F-6); **C=O** at 1636.18 (F-4), 1635.41 (F-6); **C – Cl** at 562.85 (F-4), 565 (F-6); **C – H** at 2940 (F-4), 2941.27 (F-6); **O=C=O** at 2274.28 (F-4), 2377.14 (F-6); **C – N** at 1256.21 for both; and **C – O** at 1070.98 (F-4), 1069.2 (F-6). The similarities of spectra pre- and post-granulation alluded to the fact that no significant interaction either from within the components or from processing has taken place that could snowball into instability in any of the 2 formulations even though they were processed differently. Matching DSC thermograms of AL in raw materials and granules after stability studies (Fig. 2) revealed a slight decrease in melting temperature of artemether from 89.7ºC to 87.7ºC all of which were within specification limit of 86 - 90ºC; and 133.4ºC to 131.9ºC for lumefantrine also close to recommended range of 128 - 132ºC. [14, 15] Researchers were of the opinion that a decrease in melting endotherm of materials is a sign of a decrease in crystallinity and a possibility of the materials becoming partially amorphous thus enhancing solubility among others.[16, 17]

Consequences of optimization process

The observations of stickiness of granulates to walls of die and punches were to the effects that incorporation of lumefantrine at the outer phase (extragranularly), caused high degree of stickiness of granules and led to poor appearance of final output. For example, the propensity of each formulation granules to cause stickiness expressed as % of total granules compressed was extrapolated as shown in Table 2. The outcome relegated formulations F-2, F-3 and F-5 to the background. It is also instructive to note that F-2 and F-5 had lumefantrine incorporated externally hence culpable in high stickiness observed; and only F-4 and F-6 formulations with fair granules properties and minimal stickiness were optimized to further improve appearance and aesthetics of final outcomes as results had indicated in Tables 2-4.

Micromeritic properties

Given the response variable parameters outlined in Table 3 which contained information about flow characteristics of granules of each formulation evaluated pre-compression, it was evident that all the formulations except F-2 had fairly flowing granulates that will not impede further processing. The flow rate of F-2 (0.170 g/s) was too low to support and enhance further processing such as tablet compression. On the other hand, with flow rate of other formulations especially after optimization as indicated in Tables 3-4, enough granulates would have been delivered on a continuous basis for subsequent processing thus ensuring uniformity of weight. The range of angle of repose (^{0}) of $\leq$ 30.32 supported this assertion. The bulk and tapped densities ranges as shown in Table 4 culminated in Hausner ratio of $\leq$ 1.13 that facilitated timely flow of granulates. This, coupled with Carr's

index (%) of ≤ 11.25 ensured further processing with uniform mass, as easy and swift consolidation of granulates was affirmed by progressive increase in density from bulk to tapped densities as shown in Table 4. This observation was in line with conclusions drawn by some other researchers.[9, 10, 18]

Conclusion

Irrespective of the process that each of the formulations had gone through; the outcome of bulk properties of granulates were such that quality performance was engendered at subsequent processing stage. Data from FTIR spectra and DSC thermograms alluded to stability of the formulations granulates when stored at intermediate conditions for 60 days. Other physical properties such as high level of stickiness of granulates were resolved during optimization thus leaving F-4 and F-6 as optimal formulations achieved within DS as envisaged in QbD adoption.

Competing interest

The authors declare that they have no competing interest of any type.

Acknowledgments

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

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