

Assessment of Compressive Characteristics of Some Brands of Artemether – Lumefantrine Double Strength Tablets

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Abstract

The study was aimed at comparatively evaluating the mechanical properties of some brands of artemether – lumefantrine double strength tablet (DST) products. The friability, hardness, disintegration tests, compressive stress, strain, extension and energy release at break of six randomly selected brands of DST products were evaluated using conventional pharmaceutical devices and engineering computerized Instron hardness tester. All the brands of the DST products passed the tablet friability test with values lower than 1% loss while one failed the disintegration test. Three brands exhibited hardness outcomes in the range of 1.30 to 3.26 KgF. Two brands gave energy release of 0.01 J while the others had 0 values at break. The plot of compressive stress and compressive strain for the products produce strikingly different pictogram patterns indicative of variable mechanical characteristics and drug release pattern ($P < 0.05$). The DST formulations exhibited significant differences in their mechanical characteristics at break which could result in possible differences in their bioavailability outcomes ($P < 0.05$). A standard operating procedure (SOP) is required to harmonize the outcomes of the mechanical characteristics of artemether – lumefantrine DST formulations.

Keywords: Compressive characteristics, Mechanical characteristics, Artemether – lumefantrine, Double strength tablets, Bioavailability.

1.Introduction

The manufacturing of oral solid dosage forms such as tablets have been by compression or granulation. In granulation, wet or dry granulation are employed[1]. Regardless of whether tablets are made by direct compression or granulation, the first step involves weighing, milling and mixing. Subsequent steps differ and different manufacturing protocols may be adopted when different brands of the products are to be produced[2]. The numerous unit processes involved in tableting include particle size reduction and sizing, blending, granulation, drying, compaction and if necessary, coating[3]. Various factors associated with these listed processes can seriously affect tablet properties[4][5].

Direct compression (DC) of granules or powders into tablets is the preferred manufacturing

process for pharmaceutical tablets because the process is simple to adopt and includes reduced capital, labour and energy cost[6][7]. Furthermore, fewer excipients are required for DC such as glidant, surfactant, pigments and stabilizers[8]. The key consideration in tableting however is to ensure consistent batch-to-batch production with respect to the quality parameters in a manufacturing line and bioequivalent products when different brands of the formulation in same dosage strength are considered[1][3].

Artemether – Lumefantrine was introduced for malaria treatment hinging on the World Health Organization recommendation using the artemisinin combination therapy (ACT)[9]. The national policy on the treatment of malaria in Nigeria also adopted

the use of artemether – lumefantrine amongst other ACT for the treatment of uncomplicated *Plasmodium falciparum* malaria. The available products of artemether – lumefantrine were the 20/120 mg tablets before the design of other formulations such as the dispersible tablets and dry powder for reconstitution prior to use. The double strength 80/480 mg tablet (DST) products also evolved to circumvent the large number of tablets involved in the therapeutic dosage in adults (*i.e.*, 4 tablets twice daily). The DST therefore was designed to improve compliance since the administration will be one tablet twice daily.

The licensing of generic products of the anti-malarial drug has thus meant that various manufacturing protocols may be employed where an official standard operating protocol (SOP) is absent. It is also part of the argument that manufacturers are in a competitive drive to present products with the friendliest market price for affordability. This however should be matched with the production of bioequivalent drug products[10]. This work is intended to evaluate the mechanical properties of the artemether - lumefantrine DST brands, which may ultimately influence the drug release profile.

2. Materials and Methods

2.1 Chemicals

Artemether and lumefantrine reference powder samples were obtained from Quimdis, France. Other chemicals were of analytical grade.

2.2 Methods

2.2.1 Drug sampling

Artemether - lumefantrine (DST) products were purchased between May and June, 2013 from pharmacies in Uyo, Southern Nigeria. The names of the six brands purchased were generated by random sampling from the list of commonly prescribed artemether – lumefantrine DST products. Following the purchase, information on, drug details were recorded from the product labels (Table 1).

2.2.2 Disintegration test

The test was performed using disintegration apparatus (Veego, India). Six tablets for each brand were tested. The tablets were placed in the disintegration apparatus. A volume of 500 mL of distilled water was used as the disintegration medium and the equipment maintained at a temperature of 32°C. The movement of the basket was regulated to a frequency of 28 cycles per minutes. The disintegration time was the time when all the tablet particles passed through the screen into the bulk medium.

2.2.3 Hardness test

2.2.3.1 Hardness test (Conventional)

Mosanto hardness tester (Mosanto, UK) was used. A total of ten tablets from each of the selected brands were tested for diametrical crushing test using Mosanto tablet hardness tester. Measurements were made in triplicate.

2.2.3.2 Hardness test (Geometrical)

Instron hardness tester (Instron, Germany) was used. The instrument considers the geometry of the tablet products as it applies a recommended stress of 2 mm/min and load capacity of 50 KN. A continuous loading on the tablet at the stress rate produces a computer interpreted second by second strain on the tablet. A total of two tablets were placed in the Instron hardness tester, and the mechanical properties of the tablets determined and analysed using the computerized software (Precidur Automatic Hardness Testing Software, 2008).

2.2.3.3 Friability

Tablet Friabilator (Friabilator, UK) was used. A total of ten tablets from each brand of artemether – lumefantrine tablet formulations were weighed and subjected to free fall as the machine rotated 25 times per minute. After 4 minutes, the tablets were dusted and reweighed. Friability was determined by computing the percentage weight loss as a percentage of the original weight.

2.3 Statistical analysis

Statistical analyses were performed by comparing the differences in the hardness of the tablet brands for the different parameters using student t-test. The compressive characteristics of drug products at load and at break were similarly compared. A confidence interval of P values less than or equal to 0.05 was considered significant.

3. Result

The randomly selected brands of DST for this investigation are detailed in Table 1. AL1 was found to be the most widely prescribed and known amongst the brands hence was regarded as the reference product.

The hardness test outcomes for the drug products are laid out in Table 2. Brands AL1, AL3 and AL5 exhibited hardness outcomes below 4 KgF. The friability test outcomes are laid out in Table 3. The tablet brands had lower than 1% weight loss. Table 4a and 4b gives the compressive properties of the DST products at load and at break. Figure 1-6 give the pictogram of the relationship between the compressive stress (MPa) and the resulting compressive strain (mm/mm).

Table 1: Details of the brands of antimalarial tablets studied

Product Code	Origin	Manufacturing Date	Expiry Date	Batch Number	Nafdac Reg.*
AL1	India	07/2012	06/2015	LD337	04-9927
AL2	India	08/2012	07/2015	ATMH0014	A4-3489
AL3	Nigeria	02/2013	01/2015	3B760002	A4-5641
AL4	India	12/2012	11/2015	113	A4-3799
AL5	China	04/2013	04/2016	130409	A4-1225
AL6	Nigeria	07/2012	08/2015	04	A4-3935

*Nafdac Reg.- National Agency for Food and Drug Administration and Control registration number.

Table 2: Tablet hardness for the brands of AL tablets

Product code	Range (mg)	Mean \pm SD (mg)	Comment
AL1	1.0 - 4.50	2.72 \pm 0.93	S
AL2	3.0 - 6.50	4.47 \pm 1.15	S
AL3	0.20 - 2.20	1.30 \pm 0.81	NS
AL4	3.0 - 8.0	4.70 \pm 1.72	S
AL5	2.0 - 4.40	3.26 \pm 0.80	S
AL6	7.0 - 8.60	7.94 \pm 0.52	S

*S and NS represent satisfactory and not satisfactory, respectively.

Table 3: Descriptive statistics on friability outcome for the brands of AL tablets

Product code	Percentage loss from tablets; (n=3)			Comment*
	Range	Mean	SD	
AL1	0.042 - 0.774	0.058	0.016	S
AL2	0.411 - 0.601	0.506	0.095	S
AL3	0.543 - 0.549	0.546	0.003	S
AL4	0.038 - 0.549	0.377	0.293	S
AL5	0.374 - 0.379	0.376	0.003	S
AL6	0.054 - 0.060	0.057	0.003	S

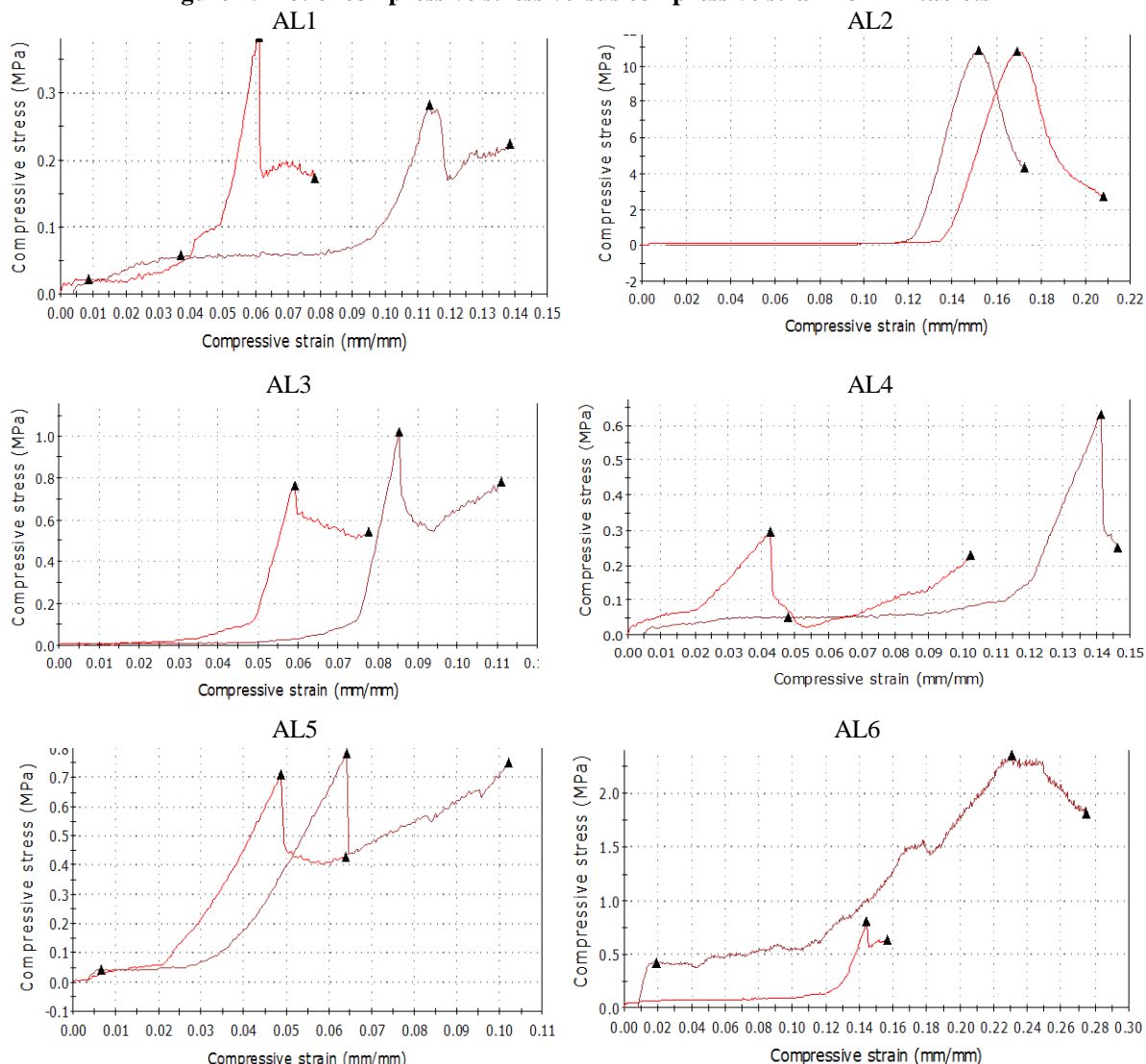
*S represents satisfactory. Official specification stipulates not more than 1.0 % loss (BP 2004).

Table 4a: Hardness parameters for the AL tablet brands using Instron hardness tester

Product code	Compressive parameters (n=3)						Energy at yield–zero slope (J)	Energy at max. load (J)
	Maximum compressive stress (MCS)	Compressive strain at MCS	Compressive load at MCS	Compressive extension at yield -zero slope (mm)	Compressive load at yield – zero slope (N)	Compressive stress at yield – zero slope (MPa)		
AL1	0.46 \pm 0.24	0.09 \pm 0.07	61.32 \pm 31.30	0.25 \pm 0.0	3.16 \pm 22.67	0.17 \pm 0.0	0	0
AL2	10.85 \pm 0.36	0.16 \pm 0.02	1440.18 \pm 4.76	0.98 \pm 0.0	1436.81 \pm 0.0	10.83 \pm 0.0	0.16 \pm 0.0	0
AL3	0.89 \pm 0.18	0.07 \pm 0.02	118.71 \pm 24.28	0.47 \pm 0.0	135.87 \pm 0.0	1.02 \pm 0.0	0.01 \pm 0.0	0
AL4	0.33 \pm 0.07	0.09 \pm 0.04	44.23 \pm 9.02	0.12 \pm 0.01	5.25 \pm 3.28	0.04 \pm 0.03	0.01 \pm 0.0	0
AL5	0.75 \pm 0.05	0.06 \pm 0.01	99.23 \pm 6.81	0.15 \pm 0.19	50.03 \pm 6.29	0.38 \pm 0.0	0	0
AL6	1.59 \pm 1.1	0.18 \pm 0.01	210.54 \pm 145.81	0.07 \pm 0.0	56.58 \pm 0.0	0.43 \pm 0.0	0	0

Table 4b: More hardness parameters for the AL tablet brands using Instron hardness tester

Product code	Compressive parameters (n=3)					
	Compressive load at break–standard (N)	Compressive extension at break –standard (mm)	Compressive strain at break – standard (mm/mm)	Compressive stress at break (MPa)	Load at break – standard (N)	Energy at break – standard (J)
AL1	31.72 \pm 2.03	0.71 \pm 0.16	0.12 \pm 0.03	0.24 \pm 0.02	31.72 \pm 2.03	0.01 \pm 0.0
AL2	468.27 \pm 147.29	1.07 \pm 0.19	0.19 \pm 0.03	3.53 \pm 1.11	468.27 \pm 147.29	0.30 \pm 0.05
AL3	87.95 \pm 22.53	0.54 \pm 0.12	0.09 \pm 0.02	0.66 \pm 0.17	87.95 \pm 22.53	0.02 \pm 0.0
AL4	26.43 \pm 4.85	0.62 \pm 0.23	0.11 \pm 0.04	0.20 \pm 0.04	26.43 \pm 4.85	0.01 \pm 0.0
AL5	78.23 \pm 30.04	0.47 \pm 0.14	0.08 \pm 0.03	0.59 \pm 0.23	78.23 \pm 30.04	0.02 \pm 0.01
AL6	162.28 \pm 110.23	1.23 \pm 0.45	0.21 \pm 0.08	1.22 \pm 0.83	162.28 \pm 110.23	0.13 \pm 0.16

Figure 1: Plot of compressive stress versus compressive strain for AL tablets

4. Discussion

The assessment of the physical properties of tablets for structural integrity will help in the preliminary evaluation of the release properties of the active pharmaceutical ingredient. The structural integrity is required to aid the tablet pass through the protocols of storage, transportation and handling before usage[11].

The mechanical properties of the DST formulations assessed by the crushing strength gives the strength of the tablet while the friability values relates to the tablet weakness. Tables 2 and 3 give the respective values of crushing strength and friability. The values for the different products varied widely indicating that the products are not from the same population. Bioequivalence of generic products primarily hinge on the parameters that determine the solubility of the active ingredients. Solubility also depends on the manner of adherence of compressed granules to the tablet matrix. The randomly selected products originated from different countries and are approved for marketing in the study area Table 1.

This makes the need for bioequivalence assessment very needful. The assessment of the mechanical characteristics of the product as was intended here is a prerequisite before bioequivalence assessment as this physical properties will preempt the success of a good bioequivalence outcome amongst a set of selected generic products. Where a detailed established manufacturing protocol does not exist for the production of generic products, the variable use of binder types and amount will certainly lead to products with different structural integrity.

The British Pharmacopoeia stipulates a disintegration time of not more than 15 min and 30 min for uncoated and coated tablets, respectively[10]. Brand AL6 failed the test and had the highest hardness test value amongst the lot. The appropriate use of binders and other excipients such as disintegrants and lubricants allow the penetration of fluid from the disintegration medium into the inner core of tablets enabling tablet structural breakdown [12].

Figure 1 gives the pictogram of the computerized capture. There was no definite identical pattern for the plot of the compressive stress versus the compressive strain for the different brands of artemether – lumefantrine DST formulations. The parameters obtained using the Instron hardness tester (*i.e.*, maximum compressive stress, compressive stress at break and energy at yield were not well correlated with the hardness test values. It was also noted that some of the products have different pictograms for the two sampled tablets indicative of variation in the compressive characteristics within a batch production. The pattern of the pictograms for AL1, AL5 and AL6 showed product of brittle nature.

The products considered here exhibited very low crushing strength indicative of brittle products hence the energy release at break for brands AL2 was zero. There is elaborate literature reference with respect to crushing strength determinations of tablets using the conventional pharmaceutical hardness testers. The use of Instron hardness tester however, enables the production of tablet formulations using same or different binders to achieve similar mechanical characteristic for a predictable and similar release pattern[13].

5. Conclusion

The mechanical strength of tablet formulation contributes to the pattern of disintegration of products and invariably the dissolution outcome. The compressive parameters evaluated using the Instron hardness tester was not correlated with the hardness test values. Attempt to achieve bioequivalent generic products, it will be necessary to monitor the compressive characteristics of the products to ensure that they have similar mechanical properties, as a first principle approach. The products of artemether – lumefantrine DST evaluated were found to have different mechanical properties and may not be expected to have comparable drug release pattern.

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