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Research Article

Quality Control Evaluation of Multi-Source Artemether-Lumefantrine Tablets Prescribed for Uncomplicated Multi-drug Resistant Malaria

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ABSTRACT

The study is aimed at evaluating the physical properties, quality control parameters and the dissolution profiles of commercial samples of artemether-lumefantrine tablets. The physiochemical parameters and assay of six brands of the products were assessed through the evaluation of uniformity of tablet weight, friability, hardness, disintegration and assay of active pharmaceutical ingredient according to established methods. The dissolution rate and disintegration time were determined in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) without enzymes. The dissolution efficiency (DE) of the tablets of the various brands was used to adjudge their likely in vivo bioavailability. All brands complied with official requirements for uniformity of weight, friability and hardness tests. The disintegration test had higher times in SIF relative to SGF. The dissolution profiles in SGF revealed that two samples attained 70% dissolution in less than 50 min while other samples in more than 1 hour. Only the innovator product, brand A, had T_{70} of 21 min and others not less than 1.5 hour in SIF. UV spectrophotometric assay of artemether content revealed only three samples containing not less than 90% (w/w) of labeled chemical content. The (DE) for the various brands was significantly higher in SIF relative to SGF ($p<0.05$). None of the brands evaluated in the study demonstrated comparable quality standards in SGF with respect to the investigated parameters. The method is simple and rugged in routine evaluation of the dissolution profiles of the brands of atemether-lumefantrine available in drug stores and could serve as a useful indicator for quality at the production line.

INTRODUCTION

Bioquivalence testing is considered as a surrogate for the chemical evaluation of the therapeutic performance of drug products [1]. Pharmaceutical equivalence of drugs may be established by in vitro studies based on measurements intended to reflect the rate and extent to which the active pharmaceutical ingredient become available at the site of action. Based on the general consideration that in vitro drug dissolution is predictive of in – vitro performance, in vitro drug dissolution test for immediate release (IR) tablets and capsules are used among other things, to ensure conformity of drug products to official or set specifications and lot-to-lot quality control [2].

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Artemisinin combination therapy (ACT) is currently the primary form of treatment for Plasmodium falciparum malaria. With the increasing resistance of falciparum malaria to conventional antimalarials and the attendant rise in morbidity in endemic areas there was the need for more potent drugs for the treatment of malaria[3]. Artemether-lumefantrine combination is the first fixed dose oral combination of an artemisinine derivative with a second unrelated antimalarial component [4-6]. Artemether [(3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12a)-Decahydro-10-methoxy-3, 12-epoxy-12Hpyrano {4, 3-j}-1, 2-benzodioxepin is a semisynthetic polyoxygenated amorphene containing a peroxide bridge that confers potent antimalarial activity. It is the o-methyl ether pro-drug of dihydroartemisinin and a derivative of artemisinin (quinghaosu), the principal antimalarial constituent of the chinese herb *Artemisia annua*. Atemether is active against the

erythrocytic stage of multi-drug resistant strains of Plasmodium falciparum [4-7].

Evidence abounds on the circulation of poor quality drugs in tropical areas of the world. Counterfeiting of drugs is also a major concern in these parts of the world (10). The proliferation of generics of antimalarial products is becoming increasingly available in many tropical countries with variable prices raising suspicion of difference in quality. Data gathered by the National malaria Control Centre has shown that recently observed widespread treatment failure of sulphadoxine, pyrimethamine and chloroquine precipitated a surge in malaria-related morbidity and mortality [8].

The objective of this work was to assess the quality control parameters, the likely dissolution profile and bioavailability of the marketed brands of artemether-lumefantrine ACT artimalarial to ascertain their quality, efficacy and safety.

MATERIALS AND METHOD

Artemether-lumefantrine brands having a label strength ratio of 20:120 (1:6) (Table 1) were purchased from drug outlets in Ikeja, Lagos, Nigeria. All tests were performed within the product expiration dates. Artemether and lumefantrine reference powders were supplied by Afrab-Chem Pharm., Lagos, Nigeria.

The reagents used were hydrochloric acid, sodium hydroxide, ethanol, monobasic potassium phosphate, acetone and sodium chloride (BDH Chemical Limited, Poole, England).

Prepared Reagents

Simulated intestinal fluid was prepared by dissolving 40g of sodium hydroxide and 34g of potassium phosphate monobasic in 2L of distilled water and then diluting to volume in a 5L volumetric flask [9].

Simulated gastric fluid was prepared by adding 43ml of concentrated hydrochloric acid to 2L of distilled water in a 5L volumetric flask; 500ml of 2ml of 2% sodium chloride solution was added and the solution was diluted to volume [9].

Visual Inspection

The shape, size and colour of the different brands of tablets were examined visually.

Friability test

Twenty tablets were weighed and subjected to abrasion using a Veego tablet friability tester at 25 rev/min.

Hardness test

The crushing strength of the tablets was determined using a Mosanto tablet hardness tester (Mosanto UK).

Uniformity of Weight

Tablets of each brand were weighed individually using a digital analytical balance (Adventure Ohaus, China). The percentage deviation of the individual tablets from the mean was determined.

Tablet Disintegration Test

Tablet disintegration was determined at 37^0C using Veego model VTDNB disintegration testing apparatus (Rutartek, India).

Assay of artemether

Standard solutions of artemether 5, 10, 20, 50, 100 mg/ml were prepared in 10ml volumetric flask. 5ml of prepared methanolic HCl was added to each and shaken up for 5 sec. This was heated in a water bath for 3 hours at 60^oC and allowed to cool at room temperature. Absorbance at 254 nm against blank was taken. Blank was prepared by heating methanolic HCl in the same conditions and diluting up to the 10 ml [10].

Dissolution Rate Determination

Dissolution rates in the simulated body fluids (i.e. SGF and SIF) were determined using a Veego dissolution rate testing apparatus in 900ml at 37 ± 0.5^0C. The basket was rotated at 100 rpm; 10ml sample was drawn at 10 minute intervals for 1h with 10ml of fresh dissolution medium replaced after each withdrawal. The UV absorbance was measured at 315nm using a UV/Vis spectrophotometer (Unico 2120, USA). The amount of artemether in the samples was determined based on the calibration curve generated at a wavelength of 254nm.

The dissolution profiles of the different brands of artemether-lumefantrine tablets were generated from the graph of the % artemether released versus time.

Statistical Analysis

Statistical analysis of the data were carried out using students t-test and results were considered significant when $p < 0.05$.

RESULTS

Table 1: The names and sources of the brands of artemether-lumefantrine in the study

Code	Brand name	Dosage Form	Manufacturer	Country of origin	NAFDAC Registration number
A	Coartem	Tablet	Norvatis	New York (USA)	04-3275
B	Artrin	Tablet	Medreich Limited	India	A4-1695
C	Artetrine	Tablet	Stallion Laboratories Pvt	India	A4-1484
D	Coatal	Tablet	Jiangsu Yixing	China	A4-1178
E	Askamether	Tablet	Naxpar Lab Pvt	India	A4-0815
F	Paluexit	Tablet	Jisngsu Ruinian pharm	China	A4-2524

Table 2: The disintegration time, hardness test, uniformity of weight and assay of the generics of atemether- lumefantrine

Brand	Disintegration Time in SGF (min)	Disintegration Time in SIF (min)	Hardness test (kg/cm^2)	Uniformity of Weight (g)	Friability test (%)	*Artemether content (%w/w)
A	2.5±0.1	3.5±0.3	1.0± 0.3	256.22±0.01	0.088	92.4±0.5
B	5.0±0.3	7.0±0.2	1.9± 0.2	243.30±0.02	0.035	53.6±0.3
C	3.0±0.3	4.0±0.1	1.1± 0.3	276.50±0.01	0.054	51.3±0.3
D	4.5±0.4	6.0±0.2	1.3± 0.4	286.34±0.02	0.032	59.3±0.7
E	6.0±0.2	6.0±0.2	3.7± 0.4	305.10±0.03	0.016	91.5±0.6
F	4.0±0.1	7.0±0.2	4.1± 0.7	273.20±0.02	0.024	97.2±0.7

*Artemether content calculated as %w/w of labeled artemether content per tablet.

Table 3: The AUC and DE of the brands of artemether-lumefantrine generic brands

Code	SIF AUC_T	SIF AUC_{40}	T_{70}	C_{40}	DE	SGF AUC_T	SGF AUC_{40}	T_{70}	C_{40}	DE
A	6957.5	2855.0	21	92	0.41	5442.5	1955.0	50	70	0.36
B	2660.0	875.0	>100	29	0.33	4460.0	1430.0	70	54	0.32
C	3132.1	1061.6	>100	39	0.34	4765.8	1591.8	60	60	0.33
D	2482.1	750.0	>100	30	0.30	6128.1	2200.3	40	50	0.36
E	2856.3	992.5	>100	35	0.35	3970.0	1220.5	90	62	0.31
F	3421.5	1041.0	>100	43	0.30	4631.6	1539.3	72	52	0.33

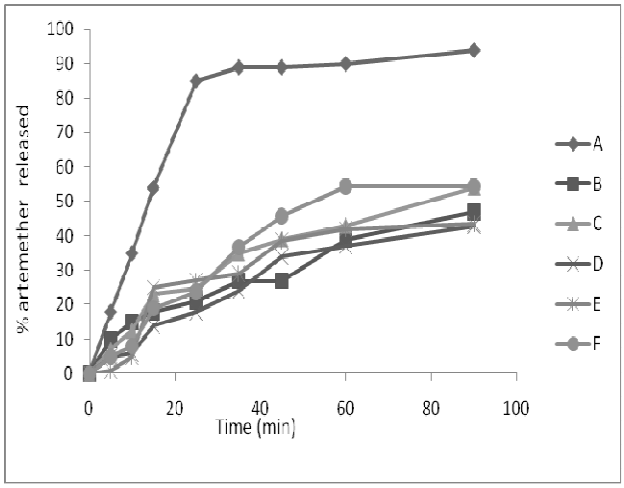

Figure 1: The dissolution profile of the brands of artemether-lumefantrine in SIF

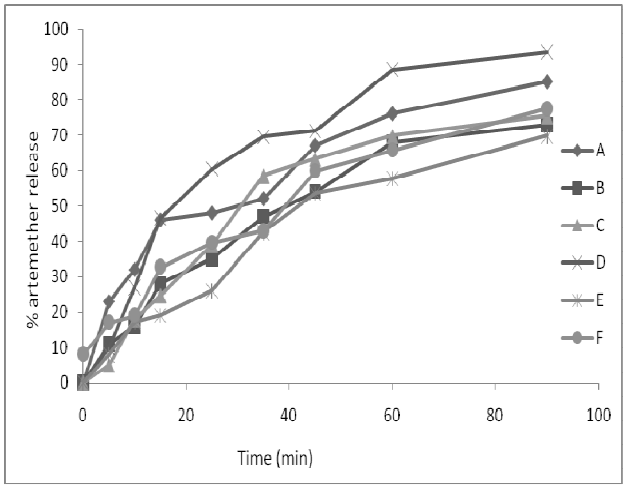

Figure 2: The dissolution profile of the brands of artemether-lumefantrine in SGF

DISCUSSION

All the brands complied with the compendia specification for uniformity of weight of not more than 7.5% percentage deviation for tablets weighing not less than 80mg and not more than 250mg. Uniformity of weight serves as a measurement of good manufacturing practices (GMP). Appropriately formed granules usually give lower variations in tablet weight as these are compacted into tablets afterwards. The hardness or crushing strength measures the physical properties of granules. It reflects the function and appropriateness of the type and quantity of binder and lubricant employed, as well as the compression force. The hardness of the brands ranged from 1.00kg/cm^2 to 4.700kg/cm^2. Brands A, B, C and D fell short of the requirement while E and F complied. Since different analytical instruments usually give varied results for crushing strength for uncoated tablets, a crushing strength of < 5 could be considered acceptable [11].

Friability is a measure of the resistance of tablets or granules to abrasion and directly on indication of the granules employed in the tablet manufacture. Friability value of 0.8 – 1% are frequently quoted as upper level of acceptance of pharmaceutical products. The products all have compliance with compendia specification of maximum of 1.0% [11].

The result proved that only brands A and E complied with the international pharmacopoeia specification for assay of range of acceptability between 90.0 – 110% (IP, 2005). Values observed for B, C, D and F were below compendia standard. According to Seiter 2005 [11], increasing numbers of substandard and fake ACT medications were detected around the world, but precise figures of the global situation is lacking. It is however estimated that more than 10% of the globally traded medicines are counterfeit [12].

The result of hardness and friability are positively correlated i.e. brands with higher hardness value exhibited minimal abrasion.

Disintegration and dissolution tests are designed to evaluate the ability of the tablet to release the incorporated active ingredients. Disintegration is directly related to dissolution and subsequently the bioavailability of a drug. A drug incorporated in a tablet is released rapidly as the tablet disintegrates. Disintegration is a very important step for immediate release (IR) dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the drug.

All brands except F, exhibited different rate of disintegration in SGF and SIF. Generally the disintegration of brands A – E was faster in SIF than SGF but brand F had an insignificantly different rate of disintegration in both simulated fluids. All brands however complied with the compendial specifications for disintegration. The B. P. specifies that unwanted tablets should disintegrate within 30 minutes in about 8 minutes, 70% of the active ingredient of the drug was released in SGF while 83% was released in SIF for product A (innovator) Brand C recorded the lowest rate of dissolution followed by F, D and G respectively. B and C showed a dissolution

pattern akin to a sustained release tablet formulation. Manufacturing methods may be the cause of differences in the performance of generics of an API. The release rates and extent of absorption of active ingredients depend largely on the excipients and the minute details of the other physicochemical properties of both excipients and drug substance [13, 14]. D and G showed a progressive increase in dissolution in both simulated body fluids. Factors that can influence the dissolution rate of drugs are particle size, the wettability, the solubility and the drug form (crystalline or amorphous) [15]. Different manufacturers are likely to adopt different methods during their tableting stages which will ultimately affect the dissolution characteristics of their product. Multiple sourced drugs may have varying performance due to the result of their dissolution behaviours. Good Manufacturing Practices (GMP) therefore involves a critical analysis of the various key factors as to control the overall outcome of dissolution. In SIF, D and F recorded the least concentration of drug release. The observation therefore calls for the investigation on the reason(s) for the poor dissolution performance of the brands when compared with the other generic brands.

CONCLUSION

Malaria recrudescence and treatment failure is possibly due to poor drug formulation processes and inappropriate release profile of drug products. The fight against malaria should include drug quality assurance as drug use remains a mainstay in malaria prophylaxis and treatment.

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