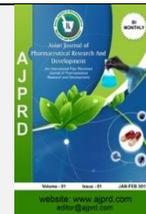


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Research Article

Quality Assessment of Antibiotic Oral Drug Formulations Marketed In Katsina State, Nigeria

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ABSTRACT

There are increasing reports on the high incidence of substandard drugs, especially in developing countries. Pharmaceutical products have been reported to contain either no, low, or excessive amounts of the active pharmaceutical ingredient (API). In view of the above, 112 samples of six different antibiotic oral drug formulations were evaluated for chemical quality by assessing the presence and the percentage content of the stated active pharmaceutical ingredients using validated HPLC assay as described in the official monograph of the British and United States pharmacopoeia. The result indicates that 43 (38.4%) had active ingredients outside the set pharmacopoeial limit and therefore were non-compliant to the BP and the USP specifications for percentage content. Ampiclox and Cotrimoxazole had the highest proportion of samples with active ingredient outside the pharmacopoeial limit, and in three samples (one Augmentin and two Ampiclox), no active ingredient was detected. The presence of API lower than the claimed content declared on the packaging was the primary cause of non-compliance. The potential implications of the use of substandard drugs are treatment failure and the development of drug-resistance.

Keywords: Antibiotics, chemical quality, API, substandard drugs, HPLC

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INTRODUCTION

There is reportedly a high incidence of the availability of substandard medicines in several developing countries¹. Antibiotics and antimalarial drugs account for the majority of products that are most often reported as substandard/counterfeit in the developing countries². The quality of medicines available in some less developed countries is inadequate in terms of the content of active ingredient³. Pharmaceutical products have been reported to contain either no, low, or excessive amounts of the active ingredient. The most common type of substandard/counterfeit antimicrobial drugs are those that have reduced amount of active drug, and the majority of them are manufactured in Southeast Asia and Africa³.

Inadequate quality drug preparations such as those that contain low amount of API have low efficacy that may result

in therapeutic failure and development of resistance. In such cases where the drugs contain excessive amounts of active ingredients, this could lead to adverse clinical events such as toxicity in patients and the implications are even more crucial for paediatric formulations^{1, 4}. In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) has identified various forms of fake/counterfeit and substandard drugs, which include drugs with no active ingredient(s) and those with insufficient active ingredients⁵.

Chemical assays are used for the identification and estimation of the level of active ingredients in pharmaceuticals⁶. Chemical assays include automated methods such as high-performance liquid chromatography (HPLC) and UV spectrophotometry⁷. HPLC is regarded as the gold standard for drug quality analysis as it offers

accuracy, specificity, and precision in quantifying the amount of stated API detected or its absence⁸.

One of the essential quality indicators of a given drug preparation is its content of the active pharmaceutical ingredient (API), a drug can be judged to be of good quality if its API is within the specification of the set pharmacopoeial limits⁴.

For being one of the enlisted drugs by the WHO model list of essential medicines⁹, antibiotics such as amoxicillin-clavulanic acid, ampiclox, ciprofloxacin, cotrimoxazole, and metronidazole remains one of the first choice antimicrobials for use in chemotherapy. They are one of the most versatile antibiotics in clinical practice in Nigeria, and for this reason, it becomes imperative to determine the quality of these products frequently administered to patients to ensure that they are safe and fit for their intended use.

MATERIALS AND METHODS

Collection of samples

A total of 112 samples of six different antibiotic oral drug formulations were collected from various drug outlets (Patent medicine stores and Hospital pharmacies) located within the state. Samples were purchased on sight and anonymously by adopting the method of¹⁰.

The samples comprised of Augmentin, ampiclox, amoxicillin, ciprofloxacin, cotrimoxazole, and metronidazole. The selection of the drugs for the study was based on their inclusion in the WHO model list of essential medicines. Information obtained from clinicians testifies that

these drugs are one of the most commonly prescribed antibiotic medications in the study area. Additionally, the selection of these drugs was based on their high usage; they represent a large proportion of total drug usage in the study area.

Evaluation of the Chemical Quality Using HPLC Assay

Assay for the content of the stated active pharmaceutical ingredients (APIs) of the samples was carried out using official monograph outlined in the United States Pharmacopoeia¹¹ and British Pharmacopoeia¹².

The assay for each drug sample and its equivalent reference standard was carried out using an ELITE-Lachrom HPLC System consisting of Ultra-Violet visible Detector L-2420, Column oven L-2300, an autosampler/injector L-2200, and a pump L-2130. The ELITE-lachrom Computer data system software generated the visual view of the chromatogram/calibration curves of each compound.

Analysis was done in replicates and mean values were recorded as a characteristic of the active ingredient content of the sample. Peak responses of the samples were compared with that of the standard. Following analyses, the drug content was calculated as the percentage of the stated amount of Active Pharmaceutical Ingredient and compared with pharmacopoeial limits specified in the BP¹² and USP 41 NF 36¹¹. The chromatographic conditions employed for the assay of the different API such as column temperature, the stationary phase, mobile phase, amount of samples injected and the detection wavelength are presented in table 1.0.

Table 1.0: HPLC Conditions Employed for the Assay of the different APIs

API	Dosage Forms	HPLC Conditions					
		Column	Mobile phase	Column temp.	Injection vol.	Flow rate	Wavelength
Amoxycillin	Capsules and Suspension	4-mm x 25-cm; 10- μ m	Acetonitrile & Buffer (1:24)		10ml	1.5mL/min	230nm
Amoxicillin and Clavulanic acid	Tablets and Oral suspension	4mm x 30-cm; 3-10- μ m	Methanol & and Buffer NaPO ₄ (1.19)		20 ml	2mL/min	220nm
Metronidazole/	Tablets	4.6-mm x 15-cm	Methonol & water (20:80)		10 μ L	1mL/min	254nm
Metronidazole benzoate	Oral suspension	4.6-mm x 15-cm; 5 μ m	Acetonitrile & Acetic acid (40:60)	30°C	5 ml	1.0mL/min	316nm
Cloxacillin	Capsules and oral suspensions	4.6-mm x 25-cm	Acetonitrile & buffer K ₂ PO ₄ (20:80)		20 μ L	1.0 mL/min	225nm
Ampicillin	Capsules	25cm x 4.6 mm; 5 μ m	Acetone & Ammonium acetate (10:90)	Ambient	50 μ L	1.0 mL/min	254nm
Ciprofloxacin	Tablets	4.6-mm x 25-cm; 5 μ m	Acetonitrile & Phosphoric acid	30°C	10 μ L	1.5 mL/min	280nm
Sulfamethoxazole & Trimethoprim	Oral suspension & Tablets	3.9-mm x 30-cm	Water, Acetonitrile & Triethylamine		20 μ L	2.0 mL/min	254nm

RESULTS

In general, a total of 112 of the sampled oral drug formulations were evaluated for chemical quality by assessing the presence and the percentage content of the active pharmaceutical ingredients using validated HPLC methods. Table 2.0 presents the proportion of sampled antibacterial oral drug formulations whose active ingredients are either within or outside the Pharmacopoeial limit as specified in the official monographs of the British and the

United States pharmacopeia. In all, 69 (61.6%) of the samples studied contained amounts of active ingredient within the appropriate limits while 43 (38.4%) had active ingredient outside the set pharmacopoeial limit and therefore were non-compliant to the BP (2017) and the USP (2018) specifications for percentage content. Ampiclox and Cotrimoxazole had the highest proportion of samples with active ingredient outside the pharmacopoeial limit, and in three samples (one Augmentin and two Ampiclox), no active ingredient was detected.

Table 2.0: Quality Assessment of the Sampled Antibiotic Oral Drug Formulations

Type of formulation	No. of samples analyzed	Number within the pharmacopoeial limit (compliant)	Number outside pharmacopoeial limit (non-compliant)
Augmentin	13	09	04 (30.8%)
Amoxicillin	34	21	13 (38.2%)
Ampiclox	07	03	04 (57.1%)
Ciprofloxacin	20	14	06 (30.0%)
Cotrimoxazole	17	10	07 (41.2%)
Metronidazole	21	13	08 (38.1%)
Total	112	69 (61.6%)	43 (38.4%)

The distribution of the sampled antibiotic oral drug formulations concerning country of origin shows that 82 (73.2%) were locally made (made in Nigeria) while 30 (26.8%) were foreign, most of which originated from India, China, Pakistan, and the United Kingdom.

Figure 1.0 shows the distribution and a comparative analysis of the quality of locally manufactured (made in Nigeria) samples of oral drug formulations versus their foreign counterparts. Of the overall 43 (38.4%) of the sampled products that had API outside the set pharmacopoeial limit,

higher proportion of these were from the products manufactured in Nigeria, 35 (31.3%) while only 08 (7.1%) of the foreign antibiotic formulations had their API outside the set pharmacopoeial limit and therefore were non-compliant.

Of the 43 samples that were substandard concerning the content of API, 36 (83.7%) had a low amount of active ingredient, while the presence of an excessive amount of API was observed in 04 (9.3%). Additionally, in 03 (7.0%) of the samples, no active ingredient was detected as present in figure 2.0.

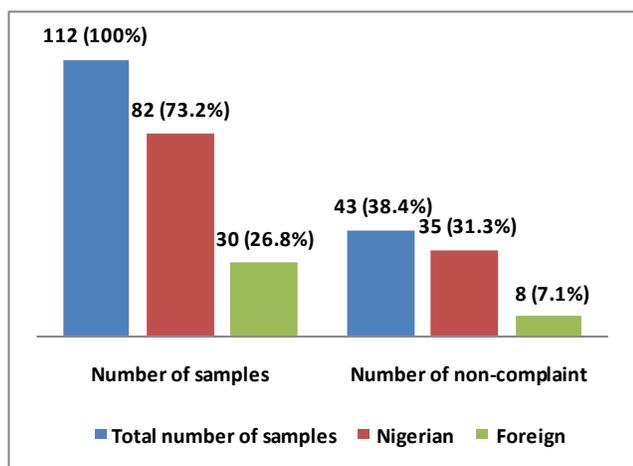


Figure 1: Distribution and the quality of locally manufactured (Nigerian) and foreign (imported) antibiotic products investigated.

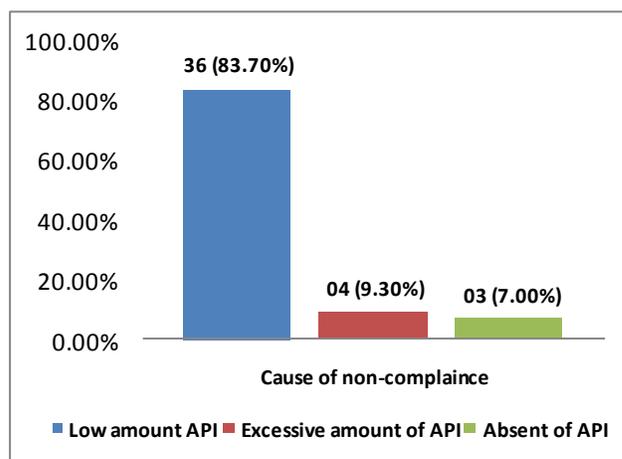


Figure 2: Present the cause of non-compliance to the pharmacopoeial limit among the substandard antibiotic oral drug formulations.

DISCUSSION

In Nigeria and other parts of the world, there have been reports of the presence of active ingredients outside the pharmacopoeial limits (1, 2, 10, and 13). In this study, 38.4% of the sampled oral antibiotic formulations had active ingredients outside the set pharmacopoeial limit and therefore were non-compliant and substandard concerning pharmacopoeial standards.

The proportion of preparations failing to comply with pharmacopoeial standards in our study is comparable to the report of ¹. In their research on drug samples available from retail outlets in Nigeria and Thailand, 36.5% of the samples were substandard with respect to pharmacopoeial limits.

Higher incidences of substandard drugs with respect to the content of API have been reported. In a study on 581 samples of 27 different drugs from 35 pharmacies in Lagos and Abuja, Nigeria reported that 279 (48%) samples did not comply with the set pharmacopoeial limits ². Similarly, a study on the quality assessment of some essential children's medicines sold in licensed outlets in the Ashanti Region, Ghana reported that 42 (61.8%) failed the official drug content test¹⁴.

Five (71.4%) of the seven samples of ampiclox capsules (ampicillin plus cloxacillin) were found to be of lower quality than the officially prescribed standards. Two (28.6%) of the ampiclox capsules had no active ingredient. A lower incidence of 57.1% substandard ampicillin formulations were reported in Jos ¹⁰, additionally, 60% of the samples of ampicillin capsules with low quality were reported ¹⁵. Likewise, in an in-vitro assessment of thirteen brands of 250mg ampicillin capsules available in Nigeria showed that 23.1% of the brands tested were substandard ¹⁶. However, there was an improvement in the quality of oral ampicillin with regards to the content of the active ingredient that circulates in Kano. The active ingredient namely ampicillin trihydrate (BP), was observed to be present in all the samples analyzed, and all the samples had percentage ampicillin content in the region of 84-101% ¹⁷.

In our study, the prevalence of substandard products of amoxicillin brands 13/34 (38.2%), is lower than the report of similar studies where 40% of Amoxicillin dry syrup and 25% capsules were substandard ². Similarly, 56% of amoxicillin capsules purchased from retail pharmacies within the Lebanese, Jordanian, Egyptian, and Saudi markets did not meet the United States Pharmacopeia (USP) requirements, and most had amounts bordering the lower limit ¹⁸. However, all the samples of amoxicillin obtained from Ghana, Nigeria, and the United Kingdom complied with U.S. Pharmacopeia (USP) tolerance limits ⁸.

Also, of the seventeen brands of Co-trimoxazole samples, seven (41.2%) samples failed to comply with the BP and USP standard. Our observation here was that four of the Co-trimoxazole samples contained the right amount of sulfamethoxazole but had an amount of trimethoprim higher than the specified limit. Three samples, however, had both sulfamethoxazole and trimethoprim above the upper limit. Similar observations were reported in a study where 29.4% of the Co-trimoxazole samples were substandard with respect

to pharmacopoeial limits (1). Another survey from Ghana reported that all the cotrimoxazole suspensions sampled failed the official drug content test ¹⁴. Moreover, 60% of tablets of co-trimoxazole purchased in Ghana and Nigeria did not comply with U.S. Pharmacopeia (USP) tolerance limits ⁸.

Moreover, 38.1% of the samples of metronidazole oral suspension and tablets failed the drug content assay. A report of a previous study has shown that all the metronidazole suspension (100%) was unable to meet up with the pharmacopoeial specifications. In all the metronidazole suspensions, no active ingredient was detected ². However, one (16.7%) of metronidazole samples studied in Ghana passed, and one failed marginally while three samples contained a much lower amount of the drug than the stipulated standard, as reported by ¹⁴.

Nine of the thirteen brands of Augmentin (Amoxicillin-Clavulanic acid) samples had the right active ingredients, as indicated by the label claim. However, 30.8% of the samples were none compliant to the BP specification for percentage content. And in one brand of the Augmentin tablets, no active ingredient was detected. However, findings of a study from Lagos, Nigeria, indicate strongly that there was an improvement in the quality of amoxicillin-clavulanate potassium tablets with regards to the content of the active ingredient by¹⁹. Similarly, in a study to evaluate the pharmaceutical quality of tablets of Augmentin brands that are available in Libyan local market found that all the analyzed drugs attain standards of quality recommended by official compendia of the United States Pharmacopeia (USP), British Pharmacopeia (BP) and European Pharmacopoeia (Ph. Eur.)²⁰.

As with other previous studies, the presence of the low amount of API was the cause for non-compliance observed in about 83.7% of the samples. In most cases, the concentration of the active ingredient is lower than the claimed content declared on the packaging. Reasons for the little amount of API observed in the samples may include poor manufacturing or transportation, decomposition, and poor storage conditions and dilution of drugs with other chemicals ³.

The potential health implications from the use of substandard drugs are of great concern. Unfortunately, the administration of such drugs could result in serious health implications such as therapeutic failure, severe adverse drug reactions, increased morbidity and mortality, high cost of treatment, development of drug resistance, and waste of resources ^{14, 21}. Where the amount of active drug is well below the stated amounts, the use of these preparations could result in serious under dosage leading to possible therapeutic failure and selection for drug-resistant organisms ².

Factors contributing to poor quality drugs in developing countries include absence of suitable manufacturing process and poor quality control, poor and uncontrolled storage conditions, such as high temperature and humidity conditions which could lead to decomposition of APIs in drugs as well as inadequate and ineffective regulations by government and its regulatory bodies significantly contribute to the increased

prevalence of substandard and counterfeit medications in developing countries²².

CONCLUSION

The presence of API outside the set pharmacopoeial limit in 38.4% of the samples has shown that a significant proportion of the oral antibiotic formulations available on sale during the study period are of poor quality. The finding of this study implies the possible therapeutic failure from the use of some oral drug formulations in the Nigerian drug market.

It is recommended that manufacturers of pharmaceutical antibiotic formulations should adhere to the guidelines of current good manufacturing practices (CGMP) strictly at any stage of production as these may significantly affect the quality of the finished pharmaceutical products. They have to ensure the production of the right quality medicines that are safe, effective and potent.

On the other hand, NAFDAC and other regulatory agencies should carry out a more vigorous approach in monitoring programs and post-marketing surveillance towards ensuring the circulation of standard drugs in Nigeria.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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