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Audit of the Physico-Chemical Quality of Amoxicillin Based Drugs Marketed in Senegal

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Abstract

Non-compliant antibiotics pose problems of therapeutic efficacy at the level of the individual, but also a serious public health problem. The objective of our study was to evaluate the quality of generic amoxicillin (42 samples) by analytical methods in Dakar/Senegal. At 100% visual inspection of compliance; 100% compliance uniformity test; at the dissolution test all > 80% (86.8% to 108.8%). The presence of amoxicillin with the following contents: Tablets (95.2% to 104.1%); Capsules (91.5% to 113.9%) and Suspensions drinkable (96.9% - 118.7%). All the samples in our study are 100% compliant according to the European and American pharmacopoeias (90% - 120%). Other studies should therefore be oriented in the direction of stability as well as the dosage of degradation products.

Keywords

Quality Control, Amoxicillin, Analytical Methods

1. Introduction

One of the major causes of global morbidity remains infectious diseases [1], specifically in low-resource countries where insufficient resources, inadequate infrastructure and poor access to health services impact disease outcomes [2]. Thus to allow access to medicines for all and at a bearable price, the Bamako initiative was adopted in 1987 by the African ministers of health during the 37th session of the World Health Organization (WHO) in Mali [3]. Amoxicillin is

part of the beta-lactam family [4]. Effective against a broad spectrum of bacteria and of low toxicity for mammalian cells [5], the use of beta-lactams represents 65% of the total world market for antibiotics [6]. A counterfeit medicine is a medicine that is deliberately and fraudulently provided with a label that does not indicate its identity and/or its true source. It can be a specialty or a generic product, and among counterfeit products, there are some that contain the right ingredients or bad ingredients or even no active ingredient and there are others where the active ingredient is in insufficient quantity or whose packaging has been falsified [7].

So far, more than 920 medical products have been reported as counterfeit, belonging to all main therapeutic classes and concerning brand-name drugs as well as generic drugs. The WHO estimates that 25% of drugs used in developing countries are counterfeit or substandard and that 5% of antibiotics sold worldwide are counterfeit [8]. Among the counterfeit medicines discovered, many cases have shown harmful health effects. In extreme cases, we can observe the aggravation of the pathologies treated [9]. Quality control is, therefore, necessary to provide populations with quality amoxicillin and limit the consequences of the use of poor-quality amoxicillin. It is in this perspective that this work falls under the general objective of which was to contribute to the evaluation of the quality of generic drugs based on amoxicillin available in Senegal.

2. Materials and Methods

2.1. Framework and Duration of Study

The experimental study was carried out at the National Laboratory for the Control of Medicines located on Avenue Pasteur opposite the Aristide Le Dantec Hospital in Dakar, Senegal. The LNCM is responsible for the technical control of the quality of medicines in collaboration with the Department of Pharmacy and Medicines. The study took place from December 2015 to March 2016.

2.2. Material

We used the following materials: a Millipore Biocel ultrapure water apparatus, a Branson model 1510 ultrasonic bath, a Sartorius model LA23OS scale, a HANSON model SR8 plus dissolutest series 02040372, a GFL series water distiller 11052203J, a Varian Pro Star HPLC 35 composed of various models (auto Sampler model 410; UV detector model 335, column oven model 510, column L1, (C18) 4 mm × 25 cm and pump model 240), a Mettler Toledo 365 Ion pH meter Analyzer (03 pH-meter19) and a UV-Vis spectrophotometer model V-570 (Spectramanager software).

Reagents

Where: Monobasic potassium phosphate, Acetonitrile, HPLC methanol and Potassium hydroxide KOH. Reference substance (SRC amoxicillin trihydrate powder).

2.3. Methods

2.3.1. Sampling

Consisted of 42 generic amoxicillin collected from four main wholesalers in Dakar. These samples are divided into: 10 tablets of 1000 mg and 500 mg; 17 capsules of 500 mg and 15 drinkable suspensions of 500 mg; 250 mg and 125 mg.

2.3.2. Visual Inspection

Primary and secondary packaging, appearance, color and smell, note the manufacturer's address.

2.3.3. Galenic Control: Dissolution Test of Amoxicillin Capsules

Is done according to the standards of USP 36 volume 2; 2013 [10].

Procedure: 06 capsules per sample were introduced individually into each of the 900 ml of dissolution medium (water) at 37˚C ± 0.5˚C; we took a sample after 60 minutes. The aim was to determine the dosage of dissolved amoxicillin from absorbances at the maximum wavelength of 272 nm on filtered portions of test solutions suitably diluted with the dissolution medium. Compare to reference material with known concentration of Amoxicillin USP RS. Tolerances: not less than 80% of the indicated dosage, dissolves in 60 minutes.

2.3.4. Identification and Assay by HPLC

Preparation of samples and standard solution [10].

NB: the tests are to be carried out on 3 test portions of the sample.

- **Diluent**: Dissolve 13.6 g of monobasic potassium in 2 liters of ultra-pure water, adjust the pH to 5 ± 0.1 with 45% KOH (M/V).
- **Mobile phase**: Made up of the following mixture: Thinner + acetonitrile (96/4).
- Preparation of the standard solution: Dissolve an exactly weighed quantity of amoxicillin RS in the diluent to have a concentration equal to 1.2 mg/ml. (Solution to be used within 6 hours).
- **Preparation of samples:**

Capsules: We look for the weight of powder corresponding to 100 mg of amoxicillin, then we add 100 mL of diluent (1 mg/mL) to pass through ultrasound then we filter.

Tablets: We therefore look for the weight of powder corresponding to 100 mg of amoxicillin, then we add 100 ml of diluent (1 mg/ml) to pass through ultrasound then we filter.

Powder for oral suspension: Dilute an exactly measured volume of amoxicillin oral suspension, freshly reconstituted according to the manufacturer's instructions to obtain a solution containing approximately 1 mg of anhydrous amoxicillin per ml, filter and inject.

The test analytic were carried out according to the conditions set out in **Table 1**.

2.3.5. System Compliance Check

Two samples of the reference substance were taken, one of which is for the preparation of the standard working solution and the other for the preparation

of the standard control solution.

- HPLC line: the standard working solution is injected 6 times to check the operation of the machine and the standard control solution 3 times to check the first sample [10].
- UV-Vis spectrophotometry: 10 repeated readings of the working standard solution were taken to check the operation of the machine and 5 repeated readings of the control standard solution to check the first test sample [10].

3. Results

3.1. Sampling

Gelules were in the majority with 40% followed by drinkable suspensions 36% and 24% for tablets (**Figure 1**).

3.2. Galenic Control

3.2.1. Visual Inspection

Upon visual inspection, all samples met the requirements of Good Manufacturing Practices for drugs. **Table 2** summarizes the results of the visual inspection.

3.2.2. Mass Uniformity

The mass uniformity of capsules and tablets was therefore in line with the standard (**Table 3** and **Table 4**).

Table 1. Chromatographic conditions.

Parameters	Values
Detector	230 nm
Column	C18 L1 4 mm × 25 cm
Flow rate	1.5 ml/min
Injection volume	10 µl

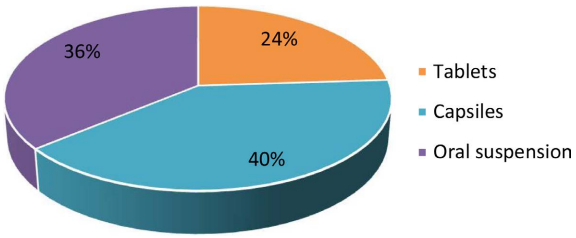

Figure 1. Breakdown of samples by dosage form.

Table 2. Results of the visual inspection.

Sample	Visual inspection
Capsiles	Burgundy red and yellow capsules. Orange and white capsules.
Tablets	White circle with a split bar on one side.
Oral suspension	White or slightly pink colored crystalline powder.

Table 3. Mass uniformity of tablets.

CODE	MAX WEIGHT (g)	MIN WEIGHT (g)	AVERAGE WEIGHT (g)	STANDARD DEVIATION (g)	CV (%)
OSP521/16 1000 MG	1.499	1.357	1.428	0.010	0.724
AMO488/16 500 MG	0.711	0.644	0.677	0.005	0.745
AMO481/16 500 MG	0.715	0.647	0.681	0.013	2.045
AMO516/16 500 MG	0.711	0.643	0.677	0.005	0.695
AMO505/16 500 MG	0.731	0.661	0.696	0.009	1.419
OSP518/16 500 MG	0.745	0.674	0.709	0.005	0.781
AMO492/1 1000 MG	1.418	1.283	1.350	0.010	0.769
OSP517/16 500 MG	0.708	0.641	0.675	0.004	0.699
OSP519/16 1000 MG	1.419	1.284	1.351	0.008	0.612

Table 4. Capsule mass uniformity.

CODE	MAX WEIGHT (g)	MIN WEIGHT (g)	AVERAGE WEIGHT (g)	STANDARD DEVIATION (g)	CV%
AMO491/16	0.638	0.549	0.593	0.011	1.855
AMO496/16	0.639	0.550	0.594	0.009	1.546
AMO490/16	0.635	0.546	0.591	0.011	1.982
AMO515/16	0.641	0.551	0.596	0.008	1.332

3.2.3. Capsule Dissolution Test

In the dissolution test all capsules in our sample were compliant with a rapid release of more than 80% in 60 min (86.8% to 108.8%). The results of capsule dissolution are shown in Table 5.

3.3. Identification and Determination of Amoxicillin by HPLC

3.3.1. Identification

The peak of standard amoxicillin was obtained at 4.84 mn (Figure 2). The peaks of the different samples emerged at the same retention time as the standard amoxicillin. The sample peaks were superimposed to the standard peak. Figure 3 represents the chromatogram of a sample.

3.3.2. Dosage

All samples conformed (90% - 120%) to specifications with recovery ranging from 91.5% to 118.7%. The results of the HPLC assay are given in Table 6.

Table 5. Results of the capsule dissolution test.

CODE	% OF DISSOLUTION	CV (%)	USP STANDARDS	CONCLUSION
503/16	108.8	3.5	≥80%	conforms
510/16	107.1	4.0	≥80%	conforms
507/16	108.8	2.4	≥80%	conforms
480/16	86.8	3.5	≥80%	conforms
504/16	94.7	4.2	≥80%	conforms
501/16	108.2	2.7	≥80%	conforms
500/16	99.9	1.5	≥80%	conforms
489/16	98.8	3.1	≥80%	conforms
499/16	94.6	2.6	≥80%	conforms
486/16	94.4	5.3	≥80%	conforms
498/16	108.3	5.2	≥80%	conforms
487/16	97.6	5.6	≥80%	conforms
490/16	103.1	2.0	≥80%	conforms
522/16	90.4	4.6	≥80%	conforms
496/16	94.6	2.6	≥80%	conforms
491/16	100.7	3.5	≥80%	conforms
515/16	106.8	3.4	≥80%	conforms

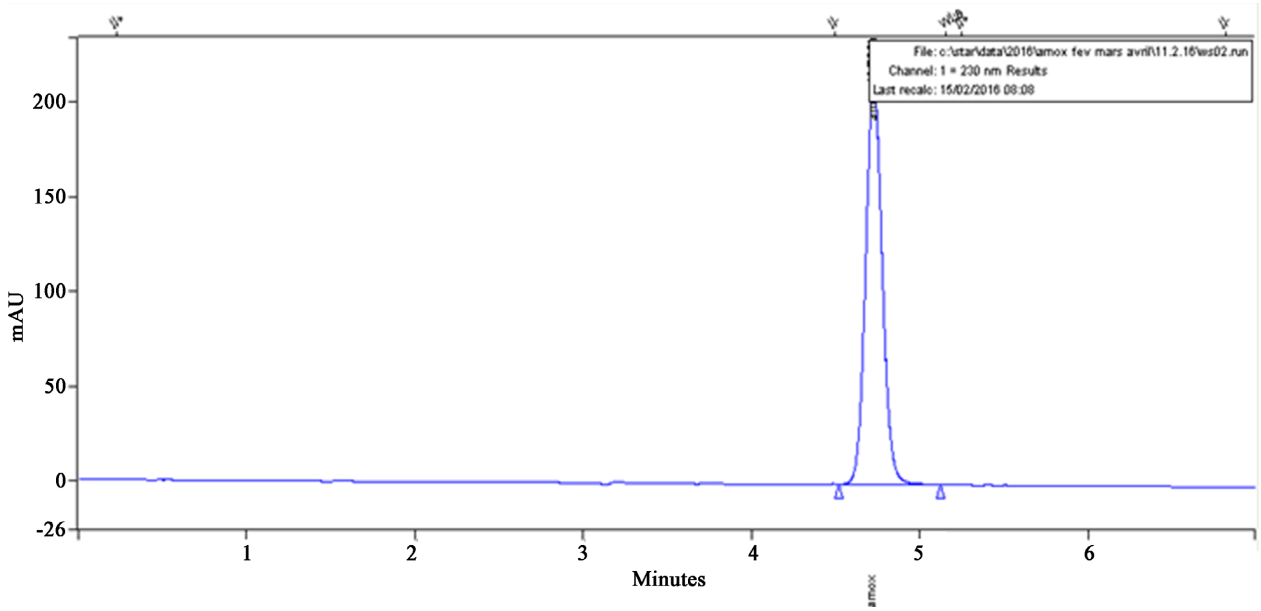

Figure 2. Chromatogram of amoxicillin standard.

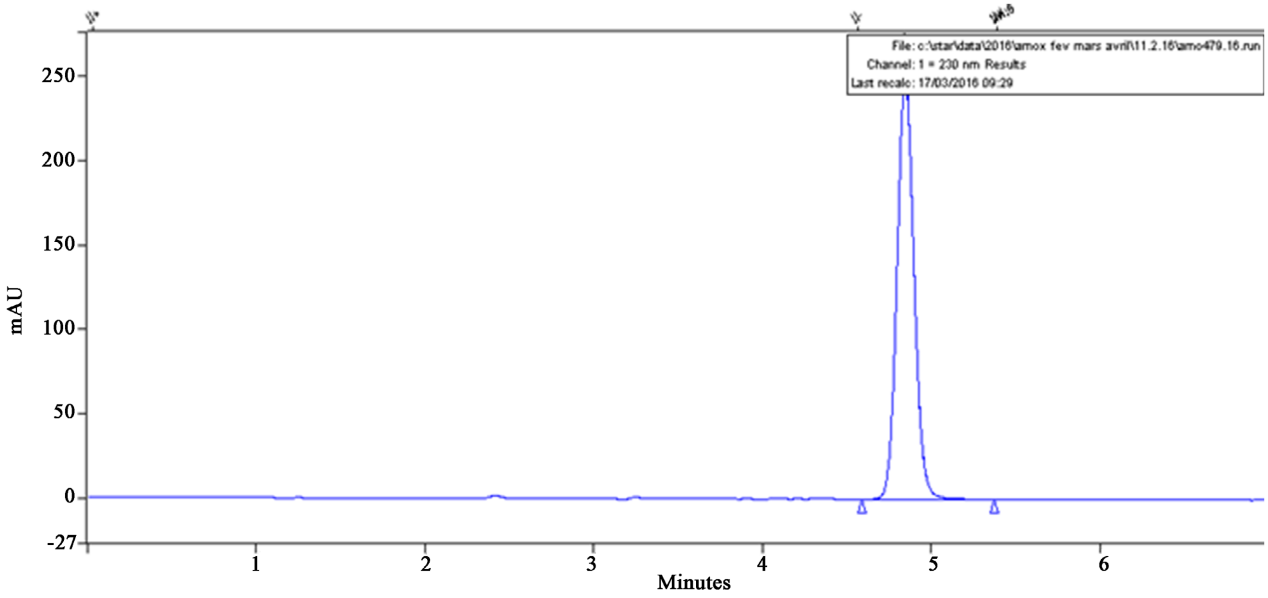

Figure 3. Chromatogram of a sample based on amoxicillin.

Table 6. Assay results.

Code	Recovery (%)	CV (%)	Standards (%)	Conclusion
479/16	96.9	1.6	[90 - 120]	Conforms
480/16	100.1	4.3	[90 - 120]	Conforms
481/16	95.2	1.2	[90 - 120]	Conforms
482/16	104.2	3.7	[90 - 120]	Conforms
483/16	118.7	7.9	[90 - 120]	Conforms
484/16	103.7	7.8	[90 - 120]	Conforms
485/16	116.2	1.9	[90 - 120]	Conforms
486/16	98.9	3.4	[90 - 120]	Conforms
487/16	97.4	3.6	[90 - 120]	Conforms
488/16	103.4	12.3	[90 - 120]	Conforms
489/16	108.0	8.2	[90 - 120]	Conforms
490/16	101.2	5.8	[90 - 120]	Conforms
491/16	96.8	0.9	[90 - 120]	Conforms
492/16	100.9	2.5	[90 - 120]	Conforms
495/16	111.3	1.6	[90 - 120]	Conforms
496/16	106.0	3.8	[90 - 120]	Conforms
497/16	110.9	3.9	[90 - 120]	Conforms
498/16	113.9	3.9	[90 - 120]	Conforms
499/16	98.6	3.2	[90 - 120]	Conforms
500/16	102.1	6.2	[90 - 120]	Conforms

Continued

501/16	103.2	8.1	[90 - 120]	Conforms
502/16	96.9	2.3	[90 - 120]	Conforms
503/16	108.3	2.9	[90 - 120]	Conforms
504/16	104.2	7.4	[90 - 120]	Conforms
505/16	104.1	3.3	[90 - 120]	Conforms
506/16	108.5	4.7	[90 - 120]	Conforms
507/16	91.5	2.2	[90 - 120]	Conforms
508/16	108.4	8.7	[90 - 120]	Conforms
509/16	109.0	12.8	[90 - 120]	Conforms
510/16	102.8	5.5	[90 - 120]	Conforms
511/16	99.9	1.5	[90 - 120]	Conforms
512/16	99.4	3.8	[90 - 120]	Conforms
513/16	104.3	5.0	[90 - 120]	Conforms
514/16	97.9	0.3	[90 - 120]	Conforms
515/16	98.5	2.8	[90 - 120]	Conforms
516/16	96.4	6.3	[90 - 120]	Conforms
517/16	103.5	5.6	[90 - 120]	Conforms
518/16	102.4	2.4	[90 - 120]	Conforms
519/16	102.7	6.7	[90 - 120]	Conforms
520/16	109.9	2.5	[90 - 120]	Conforms
521/16	103.5	5.9	[90 - 120]	Conforms
522/16	102.1	7.8	[90 - 120]	Conforms

4. Discussion

In this work, we proposed to carry out the control of the generics of amoxicillin within the framework of the follow-up of the quality. We therefore took 42 samples including 10 tablets, 15 drinkable suspensions and 17 capsules from 4 wholesale distributors in Senegal.

The primary and secondary packaging carried all the mandatory information required by good manufacturing practice. Visual analysis of the powder for odor and color criteria gave a white, crystalline powder with a characteristic amoxicillin odor. All the drugs were compliant in terms of the appearance of the capsules, the color and the smell of the powder. The study of the organoleptic characteristics revealed no apparent sign of degradation. Diop A *et al.* who detected by the visual inspection test the problems related to the presence of physical damage (breakage, dirt, cracks, foreign particles) and the absence of the expiry date [11].

Visual inspection corresponds to the requirements of good manufacturing

practices for medicinal products. This seems to show that all the samples in our study went through the normal supply circuit because GUEYE found in Senegal that nearly 67% (n = 34) of the antibiotics in the illicit sector showed non-compliance regarding labeling with absence of manufacturer's address and/or batch number [12].

The determination of the average weight and the variations in weight carried out on the capsules and tablets showed that the samples collected presented variations in weight in accordance with the standards generally accepted by the pharmacopoeias, that is to say, ±7.5% for capsules with an average weight between 300 mg and more and ±5% of tablets with a weight > 250 mg [13].

The mass uniformity of capsules and tablets is therefore in line with the standard. Thus, our study allows us to note the absence of significant variations in weight which could lead to variations in dosage (under or overdose). These results do not agree with those of Lilian C. Koech who found 13.6% failure [14].

Dissolution is an element that affects the bioavailability of the drug. Thus, a capsule or tablet that does not meet dissolution standards will necessarily have low bioavailability even with a good dosage. The dissolution test of all the capsules in our sample was compliant with a rapid release of more than 80% in 60 min (86.8% to 108.8%) [10]. All amoxicillin samples released the expected amount of active ingredient (PA) over time and met USP tolerance limits [15].

The term PA refers to a substance that has therapeutic properties. It is therefore the essential component of the drug because the presence of PA is essential for obtaining a therapeutic effect. In our study, all amoxicillin samples exhibited retention time consistent with that of reference amoxicillin. The identification therefore complies with the specifications of USP 36, which recommends a difference in retention time between the samples and their standards of ≤2% [16].

The dosage of PA guarantees the safety of the drug because the difference between a drug and a poison is the dose [17]. We cannot therefore speak of drugs when there is an underdose, even less when we are faced with an overdose. The underdosage of antibiotics is a source of resistance phenomena that jeopardize the achievements of antibiotic therapy in our developing countries.

Amoxicillin capsules, tablets and oral suspensions were assayed using high performance liquid chromatography. This assay made it possible to determine the amoxicillin content in all the samples analyzed. This assay showed that the samples have amoxicillin levels which are normal because they belong to the compliance interval which is [90% to 120%]. This result is different from that of Sherryl G. Robertson who found that 15% (28/190) did not meet pharmacopoeial requirements [18]. On the other hand, the Ecumenical Pharmaceutical Network, which found in one of the studies that 83 of the 92 samples (90.21%) were in complete compliance with the requirements of the pharmacopoeia [19].

5. Conclusions

Since amoxicillin is one of the most widely used essential drugs in Senegal and

even throughout the world, it is therefore essential to carry out the various checks before and after marketing authorization, not only to check the quality but also to also the constancy of the quality of these drugs. All samples in our study are 100% compliant with European and American Pharmacopoeia standards (90% - 120%).

This work gives a fairly clear idea of the quality of amoxicillin with 100% compliance.

We can therefore say that the use of amoxicillin in the formal sector guarantees a therapeutic result.

However, during storage of amoxicillin, degradation products or substances related to amoxicillin may appear in the product. Other studies will therefore have to be oriented in the direction of stability as well as the dosage of degradation products.

It will also be necessary to undertake studies on other commonly used antibiotics in order to guarantee our populations quality antibiotic therapy and thus limit the progression of resistant germs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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