Scientific Research Publishing

American Journal of Analytical Chemistry, 2022, 13, 449-460
https://www.scirp.org/journal/ajac
ISSN Online: 2156-8278
ISSN Print: 2156-8251

Quality Control of Paracetamol Generic Tablets Marketed in Benin and Search of Its Two Impurities P-Aminophenol and P-Nitrophenol by HPLC-UV/Visible

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How to cite this paper: Achille, Y.L., Engelbert, A.J., Gabin, A.A., Pauline, A., Parfait, D., Habib, G. and Djang'eing'a, R.M. (2022) Quality Control of Paracetamol Generic Tablets Marketed in Benin and Search of Its Two Impurities P-Aminophenol and P-Nitrophenol by HPLC-UV/Visible. *American Journal of Analytical Chemistry*, **13**, 449-460.
https://doi.org/10.4236/ajac.2022.1311030

Received: October 2, 2022
Accepted: November 14, 2022
Published: November 17, 2022

Abstract

In this work, we evaluated the quality of paracetamol generic tablets while seeking its two main impurities namely 4-para-aminophenol (4-AP) and 4-para-nitrophenol (4-NP) which have nephrotoxic and teratogenic properties. Ninety-four (94) samples were collected at various levels of the medicine supply chain and illegal markets in Benin for quality control tests such as visual inspection, pharmacotechnical tests as mass variation, disintegration test, dissolution test, followed by HPLC UV-Vis identification and assay of paracetamol, 4-AP and 4-NP. The analytes were separated on C18 Lichrocart column (250 mm × 4.0 mm i.d, 5 µm); the mobile phase was MeOH:10 mM ammonium acetate buffer pH 6.8 (35:65) pumped at a flow rate of 1 ml/min. The detection was done at 245 nm. Analysis of our results shows that 77.7% of the samples did not comply with the visual inspection test requirements, 2.1% did not pass the mass variation test, 24.3% of the sample batches didn't comply with the disintegration test requirements. In addition none of these uncomply batches passed the dissolution test, even if the identification test indicated that all samples contained paracetamol. None contained 4-NP (acceptance limit < 0.05% m/m; BP), while 3 of 94 samples contained 4-AP but within acceptance limit (4-AP < 0.1% m/m; BP). As for the paracetamol assay,

80.9% complied with the specifications of the pharmacopoeias taken as reference (90% - 110%; USP). Further, broader studies should be conducted according to the same rules of good practice for a more comprehensive analysis of the situation. Generally the quality control of paracetamol in most African countries, particularly in Benin, is based on pharmacotechnical tests and paracetamol assay. This work, in addition to the usual tests, showed the importance to search for paracetamol and other drugs' impurities during their routine quality control.

Keywords

Quality Control, Substandard Medicines, Paracetamol, P-Aminophenol, P-Nitrophenol, Benin

1. Introduction

The illicit traffic of medicines is a criminal activity expanding at global and local levels affecting the quality and safety of medicine against which many countries fight [1] [2]. According to new research from World Health Organization (WHO), 1 in 10 medical products circulating in low-and middle-income countries is either substandard or falsified [3] [4]. In West Africa, the development of land-based pharmacies for the illicit sale of medicines has made the misuse of psychotropic products among young people possible [5] [6].

Paracetamol is amongst the most frequently prescribed drugs worldwide to treat a variety of fever or pain-related conditions [7]. Its low cost and accessibility explain its hundreds of generics brands in the developing countries, and it is highly affected by counterfeit [8]. Although paracetamol is a safe and well-tolerated drug at the recommended doses, it is the most commonly overdosed drug inducing life-threatening toxicity and death [9]. Therefore, in 2008, 84 Nigerian children died from acute kidney failure after receiving falsified syrup presented as containing paracetamol in Nigeria [10]. In 2018, a study of Mazu *et al.* revealed the circulation of substandard medicinal products in Benin [11]. The illicit traffic has several consequences on public health such as therapeutic failure, increasing of the intake doses by the patient because of therapeutic ineffectiveness, misuse, toxicity, impoverishment of the population and death [12] [13]. There are several reasons for counterfeiting such as weak quality control institutions, population being mostly under informed about the consequences of falsified medicines, inaccessibility to health care and services, impoverished population, low cost of counterfeit medicines [3]. Unfortunately, substandard medicines can penetrate legal supply chain [13].

The 4-aminophenol (4-AP) is considered main co-existing impurity of paracetamol in pharmaceutical preparations originating from either synthesis or degradation [14] [15]. As 4-AP is a pharmacologically active compound possessing nephrotoxic and teratogenic effects; therefore, its concentration should be strictly

controlled [15]. 4-nitrophenol (4-NP) is the precursor of the 4-AP and is considered a potential paracetamol impurity [16]. According to British Pharmacopea 4-AP and 4-NP must be below 0.1% and 0.05% (w/w) [17]. Several methods have been reported for the assay of paracetamol and its impurities, namely 4-AP and 4-NP [18] [19] [20] [21]. However, to the best of our knowledge, the literature survey did not reveal any method for the determination of paracetamol and its two impurities for quality control. Usually the quality control of paracetamol in most African countries, particularly in Benin, is based on pharmacotechnical tests and paracetamol assay. In the present work, we evaluate the quality of paracetamol generic tablets and investigate two of its impurities such as 4-AP and 4-NP.

2. Experimental

2.1. Chemicals and Reagents

The reference standard of Paracetamol (>98.0% purity) was purchased from Certa S.A, Braine-Lalleud, Belgium. The reference standard of 4-Para-Aminophenol (4-AP) with a purity higher than 98.0% and 4-Para-Nitrophenol (4-NP) with a purity higher than 99.0% (**Figure 1**) were supplied by Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Methanol was of HPLC grade and purchased from Merck KGaA (Darmstadt, Germany). Formic acid, acetic acid, sodium hydroxyde, sodium dihydrogenophosphate and ammonium acetate, were of analytical grade and purchased from VWR Chemicals (Leuven, Belgium). Ultrapure water (H_2O) was obtained from a pure lab chorus 1 plus water purification system (Veolia, Aubervilliers, France) and used throughout the experiment.

2.2. Apparatus

The HPLC analyses were performed on an HITACHI VWR system (VWR internationnal, Pennsylvanie, USA) equipped with a quaternary pump HITACHI VWR 5160, an autosampler HITACHI VWR 5260, and an UV-DAD detector HITACHI VWR 5430. System management and data acquisition were carried out by the Chromaster software version 1.1. The Delitest Phase One Disintegration Tester Hanson; (Teledyne Hanson Research/USA) and the Dissolutest Sotax CH-4123 Allschwil/Basel; (Sotax/Switzerland) were also used.

2.3. Chromatographic Conditions

Chromatographic separation was achieved with a Lichrocart C18 column (250 mm × 4.0 mm × 2.7 µm) at 35˚C. The mobile phase consisted of the mixture of Methanol and 10 mmol/L ammonium acetate buffer pH 6.8 (35:65; v/v) with a flow rate at 1 mL/min. The column temperature was kept at 25˚C and the autosampler temperature was maintained at 15˚C with an injection volume of 10 µL. The detection wavelength was set at 245 nm with an analytical run time of 5.5 min.

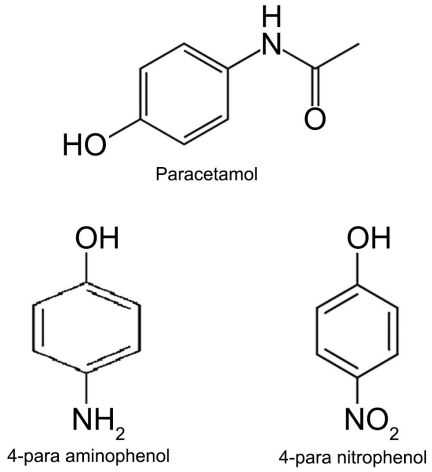

Figure 1. Chemical structure of Paracetamol, 4-para-aminophenol and 4-para-nitrophenol.

2.4. Preparation of Solutions

2.4.1. Preparation of Calibration Standard

In three 20.0 mL volumetric flasks, we introduced separately 20.0 mg of paracetamol CRS, 20.0 mg of 4-AP CRS and 20.0 mg of 4-NP CRS, which were dissolved with methanol to obtain stock solutions with concentration of 1 mg/mL and these stock solutions were kept at 4˚C. The stock solution of paracetamol was serially diluted to yield working solutions at different concentration levels from 375 µg/mL to 750 µg/mL. The stock solutions of impurities were serially diluted to yield working solutions at different concentration levels from 0.75 µg/mL to 0.125 µg/mL for 4-AP CRS and 4-NP. Calibration samples of paracetamol were then prepared with appropriate amounts of working solution diluted with mobile phase solution to obtained five concentration levels as followed 125, 187.5, 250, 312.5 and 375 µg/mL. They were filtered using a 0.45 µm Whatman paper filter. The over-all preparation was repeated in two additional days corresponding to three days (p = 3 series and n = 3 repetitions). The working temperature was ambient temperature (25˚C).

2.4.2. Solutions Used for the Assay

The test sample solutions were prepared by weighing a corresponding amount of 10 mg of paracetamol, then dissolved with mobile phase solution and diluted to obtain a final concentration of 250 µg/mL. The working solutions were filtered prior to analysis using HPLC/UV-Vis. Analysis was done in triplicate.

2.5. Method Validation

The method was validated according to the criteria developed by the "International Conference of Harmonization". The parameters evaluated to assess the reliability of the results were specificity, selectivity, linearity, precision, accuracy for paracetamol and specificity, selectivity, limit of detection and limit of quantification were assessed for impurities.

2.6. Sample Collection for Quality Control and Sample Coding

2.6.1. Sample Collection

Samples were collected from two regions namely, the "Littoral department" and the "Plateau department". The "Littoral department" is the economic hub of Benin republic with the biggest market of the country, while the "Plateau department" is a border area where medicines from Nigeria are easily found in markets. Stratified random sampling technique was used to identify the sampling outlets from selected departments. Sample collection was done from facilities at different levels within the drug distribution chain in Benin.

Level I: importers' warehouses, central and regional medical stores, Wholesale Distributors (Importer or manufacturer).

Level II: public pharmacies and hospital pharmacies.

Level III: Regulated dispensaries: Includes retail pharmacies, hospitals, health centers, dispensaries, clinics, Maternity Homes, treatment centers.

Level IV: Unauthorized outlets: (outlets or facilities selling medicines outside the approved distribution system) including informal or illegal market (open market, stalls, and mobile medicine peddlers etc). The samples were collected as mystery shoppers.

The inclusion criteria were tablet formulations at 500 mg of paracetamol generics, monotherapy, whereas exclusion criteria were the formulation with two or more active pharmaceutical ingredients, or other pharmaceutical formulations. The metadata obtained as schematized in **Figure 2** were encoded using Excel file for Windows version 16. The theoretical sample size (N) was calculated considering the general formula of sampling size (see Equation (1)).

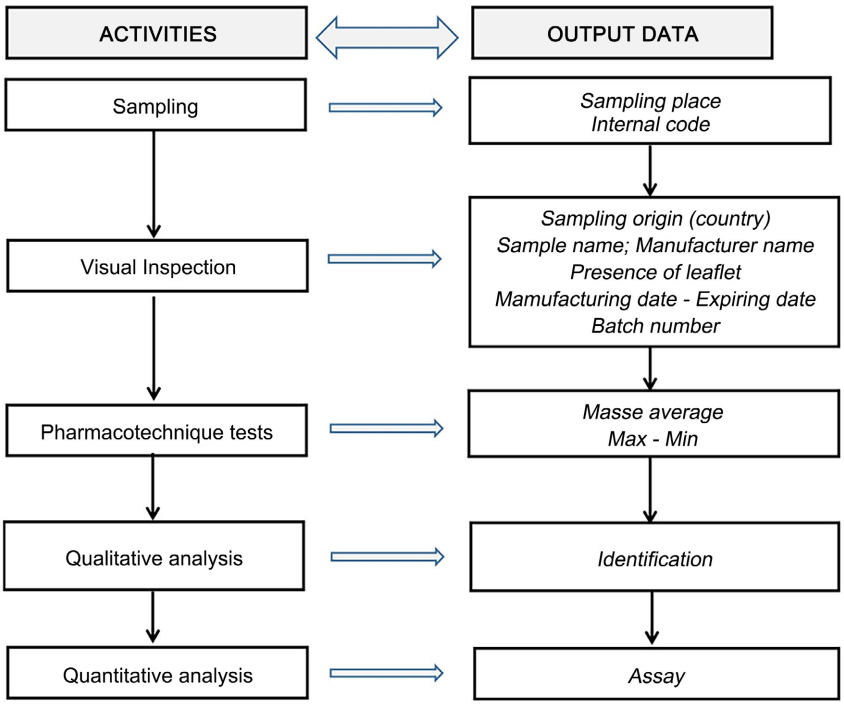

Figure 2. Sampling strategy (scheme and analyses) [4].

$$N = p(1-p)z^2/E^2 \quad (1)$$

where p is the prevalence, z is the confidence interval, and E is the margin of error with 95% confidence interval.

2.6.2. Database for Quality Control

Several quality Control tests were done for quality control survey on those samples where we collected the following data entries: 1) sampling places including the date, administrative and health sectors, 2) the findings of visual inspection according to WHO guidelines including country of origin, sample trade name, manufacturer name, packaging, labeling, and physical appearance of tablet characterized by specific size, shape and color, and license status in Benin, shelf life, presence of leaflet, 3) the findings of physico-chemical tests including mass variation, disintegration test and dissolution test, identification and assay of API and impurities using our developed method (**Figure 2**).

2.7. Statistical Treatment

The linearity of the responses of paracetamol was assessed from a scatter plot. The regression lines were determined according to the least square's method. An analysis of variance (ANOVA) was performed to test the statistical significance and the overall slope of the regression line. The repeatability or precision was assessed through the relative standard deviation (RSD) calculated from the ratio of the standard deviation to the mean of each series of measurements. The accuracy was assessed through the relative error (RE) of each series of measurements.

3. Results

3.1. Method and Validation

3.1.1. Selectivity

The selectivity of the method was determined by analyzing blank controls. It was found that no interference appeared at the retention times of paracetamol, 4-AP and 4-NP which are 2.8 min, 2.3 min and 8.2 min respectively (**Figure 3**). Typical chromatograms of paracetamol (**Figure 4**), 4-AP (**Figure 5**) and 4-NP standard solutions (**Figure 6**), and a mixture of paracetamol, 4-AP and 4-NP standard solution (**Figure 7**), were shown, respectively.

3.1.2. Linearity, Accuracy and Precision

The calibration curves were linear over the concentration range of 125 - 375 μg/mL with (R^2 = 0.9992) for paracetamol. The typical regression equations of the calibration curves were f = (21207) × C + (27333) for paracetamol, where f represents the chromatographic peak area of the analytes and C represents the concentration of the analytes.

Validation samples of six replicates of QC samples were prepared and analyzed in three separate analytical batches to evaluate the precisions and the accuracy of the method. The precision (RSD) and accuracy (RE) for the analysis of paracetamol were summarized in **Table 2**. The limits of detection and quantifi-

cation were found to be 0.0625 and 0.125 µg/mL for 4-AP and 0.1 and 0.25 µg/mL for 4-NP. The method was accurate and precise.

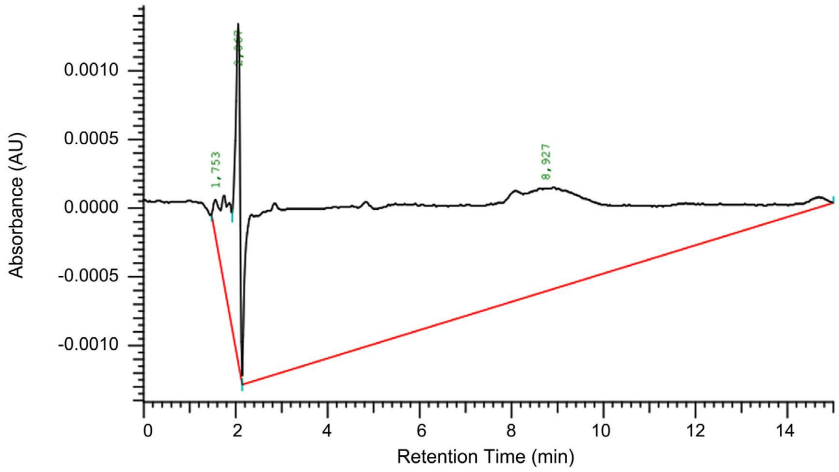

Figure 3. Chromatogram of a blank.

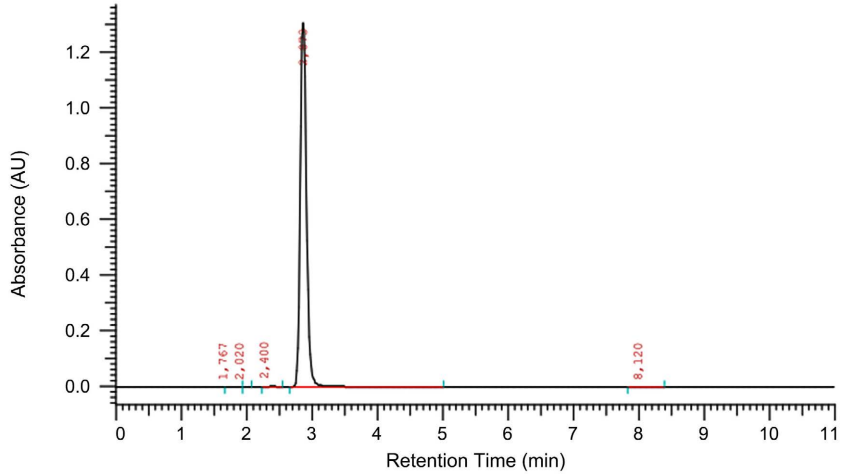

Figure 4. Chromatogram of a standard solution containing paracetamol at 125 µg/mL.

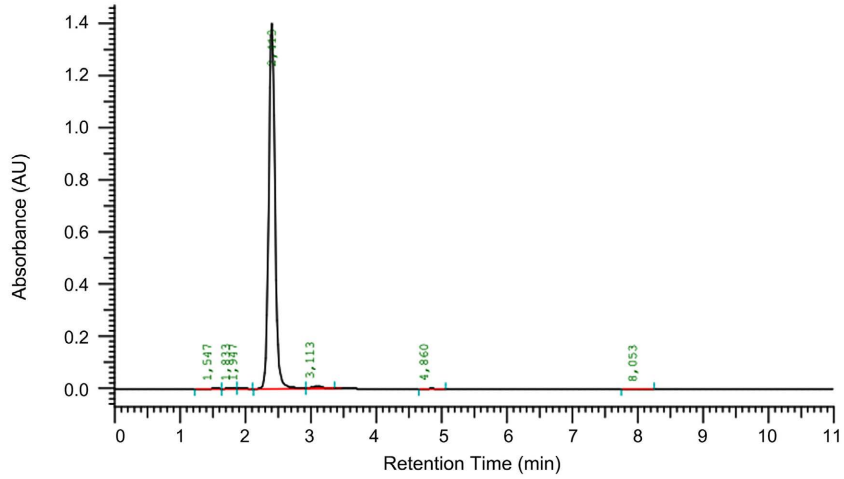

Figure 5. Chromatogram of a standard solution containing 4-AP at 0.5 µg/mL.

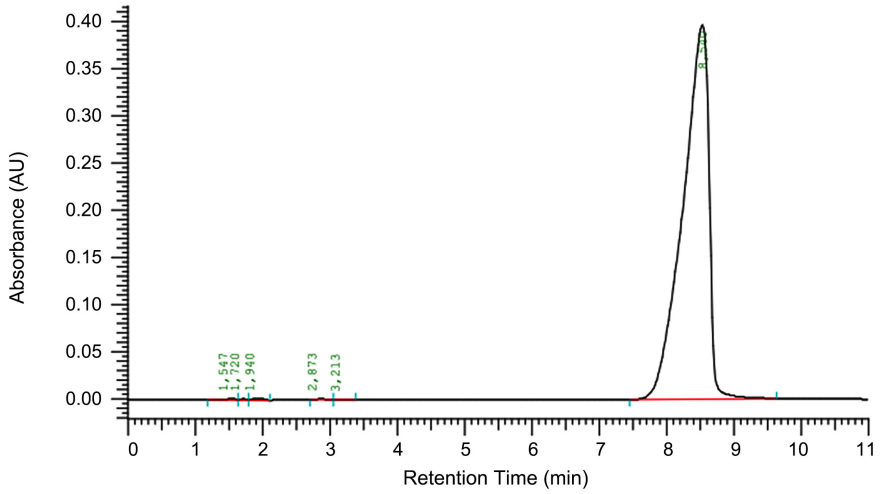

Figure 6. Chromatogram of a standard solution containing 4-NP at 0.5 µg/mL.

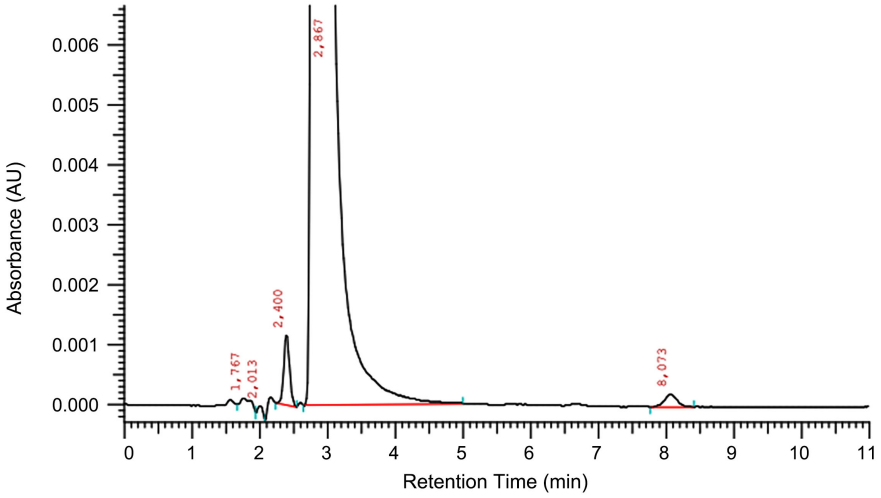

Figure 7. Chromatogram of a standard solution containing a mixture of paracetamol, 4-AP and 4-NP.

Table 1. Precision (RSD) and accuracy (RE) data for the analysis of paracetamol.

	Concentration levels (µg/mL)	Concentration added (µg/mL)	RSD (%)		RE (%) Accuracy
			Intra-day	Inter-day	
Paracetamol	Low QC	200	0.2	1.5	0.8
	Middle QC	250	0.1	1.3	0.7
	High QC	300	0.1	1.8	1.1

Table 2. Distribution of samples by site of collection.

	Littoral	Plateau	Total
Legal sector	58	23	81
Illegal sector	11	02	13
Total	69	25	94

3.2. Routine Analyses

3.2.1. Sample Collection

The targeted sample size (N) was 94 samples calculated considering the general formula of sampling size (see Equation (1). The 94 samples collected were from nine (9) trade name with 86% from legal sector and 14% from illegal sector. Those samples were collected from private sector as well as public sector (Table 2). On the other hand, 41% of sampling sites kept medicines between 25˚C and 30˚C while 59% stored medicines above 30˚C. None of them kept medicine below 25˚C.

3.2.2. Findings of Visual Inspection

We found that 22.3% of samples' internal packaging did not provide storage conditions of the medicine and 22.3% were without leaflet information. About 67% of samples were without complete manufacturer address while tablets of 21.27% of samples were without breaking lines. All sample's packaging provided the amount of active ingredient, the expiry date and batch number. The majority (45.0%) of the samples were from China, one of the largest drug producers in the world, 22.0% from Ghana, 11.0% from Benin, 11.0% from India and 11.0% from others countries. Two (2) samples were from unknown origin, that is, non-conformity. On the other hand, most medicines found in the illegal sector were without any marketing authorization in Benin except one which had marketing authorization. 1.06% of sample presented an abnormal color. As results, 77.7% of the samples did not comply with the visual inspection.

3.2.3. Findings of Physico-Chemical Tests

Concerning the mass variation, 92 samples had acceptable mass variations that were less than 5% against 2 samples (2.1%) which were not conform. Those 2 samples came from illegal sector as well as legal sector. Referring to the disintegration and the dissolution test, 24.3% of samples didn't comply with the disintegration and the dissolution test as well. That non conformity was found to be 12.5% in the legal sector and 12% in illegal sector.

3.2.4. Identification and Quantification

The developed method was successfully applied for simultaneous identification of paracetamol and its impurities 4-AP and 4-NP followed by quantification of paracetamol in paracetamol tablets. All 94 samples were compliant in terms of paracetamol identification. The concentrations of paracetamol were calculated using the calibration lines. The concentration of paracetamol range from 154 to 374.2 µg/mL. We found that 11 samples (11.7%) were under-dosage, 2 samples (2.1%) were over-dosage, while 86.2% (81 samples) were conform in paracetamol content (90.0% - 110.0%; USP). The 4-AP was detected in three 3 samples but below the specification (PAP < 0.1%, w/w; BP); while no samples contained 4-NP (specification < 0.05%, w/w; BP).

4. Discussion

Our study included 94 samples, a large population size when compare with

those of Awono *et al.,* 2021 in Cameroon and Assamoa *et al.,* 2016 in Ivory Coast who worked on eight (8) samples and nineteen (19) samples respectively [22] [23].

From the analysis only 22.3% of our samples passed the visual inspection test with a non-conformity of 77.7%. It should be noted that all the samples from the illicit sector did not pass the visual inspection test. This finding is similar to that reported by Awono *et al.* in 2021 [22]. Medicines that do not comply with visual inspection tests may present risks of intoxication, misuse, degradation of the active ingredient and therapeutic failures. Our results showed that 2.1% of the samples failed the mass variation test.

In addition, 24.32% of the sample batches showed a disintegration time or disintegration time higher than the specification standard; with 24.3% non-conformities in the formal sector and 33% non-conformities in the illegal sector. It was noticed that all the non-conformities about disintegration test found in the formal sector came from one and same brand. Our results are different from those reported by Awono *et al.* for the formal channel [22]. However, they are close to the 25% reported for the informal circuit.

All samples (100%) contained the paracetamol as active ingredient. These results are similar to those reported by Assamoa *et al.* in 2016 in Ivory Coast [23]. One sample from illegal sector presented a high over-dosage about 150% of the therapeutic dosage. These are critical and dangerous for the patients.

Regarding impurities, 3.20% of the samples contained traces of 4-AP and none contained 4-NP. These results are similar to those of Hassan *et al.* in Nigeria in 2019 where 6.67% of samples contained 4-AP. Meanwhile, those results are different from those reported by Olajire *et al.* in Nigeria in 2019 indicating high levels 0.15% and 0.21% (w/w) of 4-AP above the tolerated limit in 14 samples in Nigeria in 2019 [21]. Finally, more than half sites kept the medicines at temperature above 30˚C which is not good for the product stability and safety.

5. Conclusion

This study confirms the reality of the circulation of substandard drugs in Benin. Generally, the quality control of paracetamol in most African countries such as Benin, is based on pharmacotechnical tests and paracetamol assay. This work, in addition to the usual tests, showed the importance to search for impurities for paracetamol and for others drugs during their routine quality control. The authorities in charge of pharmaceutical regulation might increase the drug quality control in Benin and in developing countries to guarantee drug effectiveness, quality and safety for the population.

Acknowledgements

This work was done with the financial support of "Fondation Pierre Fabre".

Conflicts of Interest

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

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