

Regulatory Compliance and Associated Quality of Amoxicillin in Drug Retail Outlets of Southwestern Ethiopia

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Background: While the research findings confirm the existence of private drug retail outlets that do not comply with regulatory standards in many low-income countries, there are a lack of reports that evaluate the quality of medicines obtained from these firms. Therefore, the aim of this study was to evaluate the regulatory compliance of the retails and associated quality of amoxicillin in Southwestern Ethiopia.

Methodology: Forty-two drug retail outlets in Jimma town were evaluated using an inspection checklist developed by the Ethiopian regulatory authority, and dispensers from these retail outlets were interviewed using the pretested structured questionnaire. The drug outlets were coded and categorized into noncompliant and compliant drug retail outlets. The physicochemical quality of amoxicillin capsules obtained from these retail outlets were evaluated following methods described in the US Pharmacopoeia.

Results: The present study revealed that about 54.76% drug retail outlets were compliant with the regulatory standard. Factors like income of retail outlet, experience of dispenser, and training regarding good storage practice were associated with status of regulatory compliance (p -value <0.05). The identification, dissolution, and assay results indicated that all amoxicillin samples obtained from both noncompliant and compliant drug retail outlets complied with pharmacopoeial specification limit. Besides, the independent unequal variance t -test revealed that there is no significant difference between mean dissolution and assay of API of the amoxicillin samples obtained these drug retail outlets (p -value >0.05).

Conclusion: The regulatory compliance of private drug retail outlets in Jimma town is not satisfactory. Moreover, the laboratory findings revealed that all samples of amoxicillin capsules complied with pharmacopoeial specifications acceptance for packaging and labeling information, identification, assay, and dissolution. However, despite the fact that assays of the amoxicillin from retail outlets are within the required specification, the assays of amoxicillin obtained from noncompliant retail outlets appears to be slightly degraded, which may potentially demonstrate the impact of noncompliance of the drug retail outlets on the quality of medicines.

Keywords: drug retails, regulatory compliance, quality, amoxicillin, Ethiopia

Introduction

Ensuring the quality of medicines throughout their life cycle requires the effective monitoring of medicines at various levels from manufacturing to the end users to protect public health.^{1,2} As such, the World Health Organization (WHO) has established the regulatory standards for Good Pharmacy Practice that define the scope of practices, identifies who can practice, sets competency standards, and allocates resources to ensure their regulatory compliance.^{3,4} Thus, these regulatory

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standards are crucial to monitor pharmaceutical firms, particularly the private drug retail outlets to ensure all pharmaceutical products on the market are safe, effective, and consistently meet approved quality standards.^{5,6} The private drug retail outlets are principal players in promoting access to medicines in low- and middle-income countries.^{7,8} They have gained prominence in recent years with global initiatives, such as the affordable medicines facility for malaria (AMFM), exploring ways of utilizing them as a vehicle for expanding coverage for essential health services.⁹ The rising interest in drug retail outlets has resulted in increased frequency of interventions targeting their performance. Accordingly, the care-seekers reportedly choose the private drug retail outlets sector over the government health facilities because these drug retail outlets are more accessible, provide quicker service, and have more reliable drug stocks, are courteous and approachable, and in some cases are less costly.¹⁰ However, widespread regulatory infringement has been reported in private drug retail outlets, especially in developing countries.^{11–18} In these retail outlets, personnel requirements, structural design features for the premises, minimum equipment and material requirements, and provisions for good medicine storage and dispensing practices did not fully meet the regulatory standards of those countries. Conversely, while these findings confirm the existence of private drug retail outlets that do not comply with regulatory standards in many low-income countries, there are a lack of reports that evaluate the quality of medicines obtained from these retail outlets. From a recent report, amoxicillin capsules were highly affected by storage conditions,¹⁹ and the compliance assessment of the drug retail outlets to the regulatory standard was previously recommended in Ethiopia.²⁰ Therefore, the quality of amoxicillin 500 mg capsules was evaluated using methods mentioned in US Pharmacopeia after assessment of regulatory compliance of the drug retail outlets in Southwestern Ethiopia to decrease a risk of having poor quality amoxicillin in pharmaceutical retail outlets.

Methodology

Study Design, Period and Location

A facility based cross-sectional study design was employed among drug retail outlets in Jimma Town from March to April, 2020. Jimma town is located at 352 km from the capital, Addis Ababa. According to Central Statistical Agency (CSA) report the projected population

of Jimma zone from 2014 to 2017 is estimated to be 2,986,957.²¹ Jimma is a relatively large town with nine legally operating wholesalers of pharmaceutical products which are currently supplying pharmaceutical products to drug retail outlets (n=57), health centers (n=4), clinics (n=15) and hospitals (n=2). Moreover, the experimental work was conducted in Jimma University Laboratory of Drug Quality (JuLaDQ).

Equipments, Chemicals and Reagents

The HPLC RP system (mode: LC; column: 4 mm × 250 mm; packing L1; detector: 230 nm; flow rate: 1.5 mL/min; and injection volume: 10 µL, analytical balance, dissolution apparatus, UV spectrophotometer, pH meter, and thermometer were used. Monobasic potassium phosphate, acetonitrile HPLC grade, potassium hydroxide water HPLC grade, amoxicillin RS (secondary or working standard) and amoxicillin samples were used.

Sample Collection and Procedure

All private drug retail outlets were selected for observational study. Amoxicillin 500 mg capsules were sampled using sampling strategy which is defined following the Medicine Quality Assessment Reporting Guidelines (MEDQUARG) as proposed by Newton et al²² based on the following question. Is there a difference in quality of medicines from among the different levels of drug retail outlets? Before experimental study was carried out, 42 drug outlets were evaluated using an inspection checklist developed by the Ethiopian regulatory authority, and dispensers from these outlets were interviewed using the pretested structured questionnaire to assess the background of the dispensers and drug retail outlets. Based on the results from the observational study, the outlets were coded and categorized into noncompliant and compliant drug retail outlets based on the overall computed mean. Then, six drug retail outlets (n=6) were selected from both noncompliant (n=3) and compliant drug retail outlets (n=3) using convenience sampling method. The same brands of six samples of amoxicillin 500 mg capsules were collected from each of the selected drug retail outlets. Finally, all samples were transported to Jimma University Laboratory of Drug Quality (JuLaDQ) on the same day of sample collection. For all samples, the visual and physical inspection for labeling and packaging was performed before physicochemical quality testing. After that, identity, dissolution test, and assay for the content of active ingredient of amoxicillin 500 mg capsules were performed using the methods described in the US Pharmacopeia.²³

Specific Test Method

Physical Characteristics, Packaging and Labelling Information

Visual inspection of the physical characteristics of dosage form, packaging and labelling information was performed following the WHO checklist designed for health professionals to carry out visual inspection of medicines for signs of counterfeiting.²⁴ As such, the capsules of all samples were checked for signs of moisture, dirty marks, embedded surface spots and presence of empty capsules.

System Suitability

System suitability test was performed routinely before sample analysis could commence according to the European Pharmacopoeia method. It is undertaken to verify resolution, column efficiency and repeatability of a chromatographic system to guarantee its competence for a particular analysis.

Identification

Identification tests were performed as per USP²³ test method. The retention time of the major peak of the sample solution was checked for correspondence to that of the standard solution, as obtained in the assay.

Assay of Amoxicillin

Assay test of amoxicillin capsules was determined based method given in the US Pharmacopoeia.²³

Buffer and Mobile Phase Preparation

The buffer solution was prepared by dissolving 6.8 g/L of monobasic potassium phosphate in water, and adjusted with 45% (w/w) solution of potassium hydroxide to a pH of 5.0. Then, acetonitrile and buffer (1:24) were used for preparing mobile phase.

Preparation Sample and Standard Solution

The contents of NMT (not more than) 20 capsules were removed and completely mixed together. Then, the amount equivalent to 200 mg of anhydrous amoxicillin was dissolved in a 200-mL volumetric flask. The buffer was added to the volume, and sonicated as necessary to ensure the completion of the dissolution. Finally, 1.2 mg/mL of USP amoxicillin RS was prepared in buffer solution.

Dissolution

The dissolution test of amoxicillin capsules was determined based on the method given in the US Pharmacopoeia. Dissolution apparatus II was set to 75 rotations per min (rpm) and temperature was maintained at

37°C±0.5°C for a duration of 60 min. The set volume of 900 mL of distilled water was used as a medium. The labelled amount of amoxicillin dissolved was compared with tolerances of the test according to USP which is not less than 80% (Q).

Statistical Analysis

Data was entered, cleaned, edited for any errors and analyzed by using Statistical Package for Social Science (SPSS) version 21.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were computed. Graphs, tables, and numerical summary measures were used to display analysis of the results. Fisher's exact test was employed to determine nonrandom association between independent variables and outcome variables. Moreover, independent unequal variance *t*-test was used to determine significant difference between mean assays of amoxicillin samples, and mean drug release of amoxicillin sample at 60 min obtained from noncompliant and compliant drug retail outlets.

Operational Definitions

Noncompliant: drug retail outlets that possess a score less than the overall mean.

Compliant: drug retail outlets that possess a score greater than or equal to the overall mean.

Status of regulatory compliance is the position of drug retail outlets whether compliant or noncompliant retails.

Results

Background of the Dispensers and Drug Retail Outlets

Out of 57 drug retail outlets allowed to participate, 42 were evaluated and associated dispensers responded, with a response rate of 74%. Among the studied retail outlets around 38% of them were owned by nonprofessional personnel. The results revealed that all retail outlets were licensed and the licenses were valid. Moreover, around 54% of drug retailers had service >10 years. Regarding the status of the dispenser working in the drug retail outlets only 7.1% were noncertified dispensers. Among study dispensers, the majority had experience of <10 years. Concerning training on the storage practice of drugs, the majority of dispensers (57%) had no training related to drug storage practice (Table 1).

Table 1 Background of the Dispensers and Drug Retail Outlets (n=42)

Variables		Frequency	Percentages
Is a drug outlet licenced and valid?	Yes	42	100
	No	0	0
Owner of the drug retail outlet	Professional dispenser	26	61.9
	Nonprofessional dispenser	16	38.1
Service year of the drug retail outlets	<10 years	19	45.2
	>10 years	23	54.8
Estimated income generation per month in Ethiopian birr	<5000 Ethiopian birr	19	45.2
	>5000 Ethiopian birr	23	54.8
Status of the dispenser working in the drug retail outlets	Certified dispenser	39	92.9
	Noncertified dispenser	3	7.1
Experience of dispenser	<10 years	22	52.4
	>10 years	20	47.6
Compliant regarding licensing requirements for drug retail outlets	Yes	12	28.6
	No	30	71.4
Do you have training regarding good storage practice?	Yes	18	42.9
	No	24	57.1

Evaluation of the Drug Retail Outlets for Regulatory Compliance

The status of regulatory compliance of drug retail outlets according to the Ethiopian regulatory standard checklist out of 100% showed the overall mean of 51.46 ± 10.981 (Figure 1). Besides, the dichotomized level of compliance of drug retail outlets based on the overall mean revealed about 54.76% were compliant to regulatory standard (Figure 2).

Factors Associated with Regulatory Compliance of Drug Retail Outlets

Fisher's exact test revealed that types ownership, income per month of the drug retail outlets, experience of dispenser, and training regarding good storage practice were associated with status of regulatory compliance of drug retail outlets (Table 2).

Physical Characteristics, Packaging and Labelling Information

The physical characteristics, packaging, and labelling results showed that all the tested amoxicillin samples had no signs of moisture, dirty marks, embedded surface spots, or presence of empty capsules.

The packaging and labelling of all samples meets the minimum requirement required by the World Health Organization for packaging and labelling.

Identification and Assay of the Amoxicillin

The retention times of the major peaks in the chromatograms of all samples of amoxicillin capsules obtained were similar to that of the amoxicillin reference standard. The assay result of amoxicillin capsules for tested samples from compliant drug outlets ranged from 96.1% to 98.0% while samples obtained from noncompliant outlets ranged from 92.6% to 98.2%. Moreover, all tested samples comply with Pharmacopoeia specification, and independent unequal variance *t*-test revealed no significant difference between mean assay of amoxicillin samples obtained from compliant and noncompliant drug retail outlets (*p*-value >0.05) (Table 3).

Dissolution

The calibration curve revealed the presence of strong positive relationship ($R^2 = 0.9954$) between the concentration and absorbance over the RS amoxicillin concentration range of 444.44 to 666.66 $\mu\text{g/mL}$ (Figure 3). Cumulative amoxicillin samples released at 60 min were determined from the calibration curve constructed by RS amoxicillin using UV-visible spectroscopic method. All tested samples comply with Pharmacopoeia specification, and independent unequal

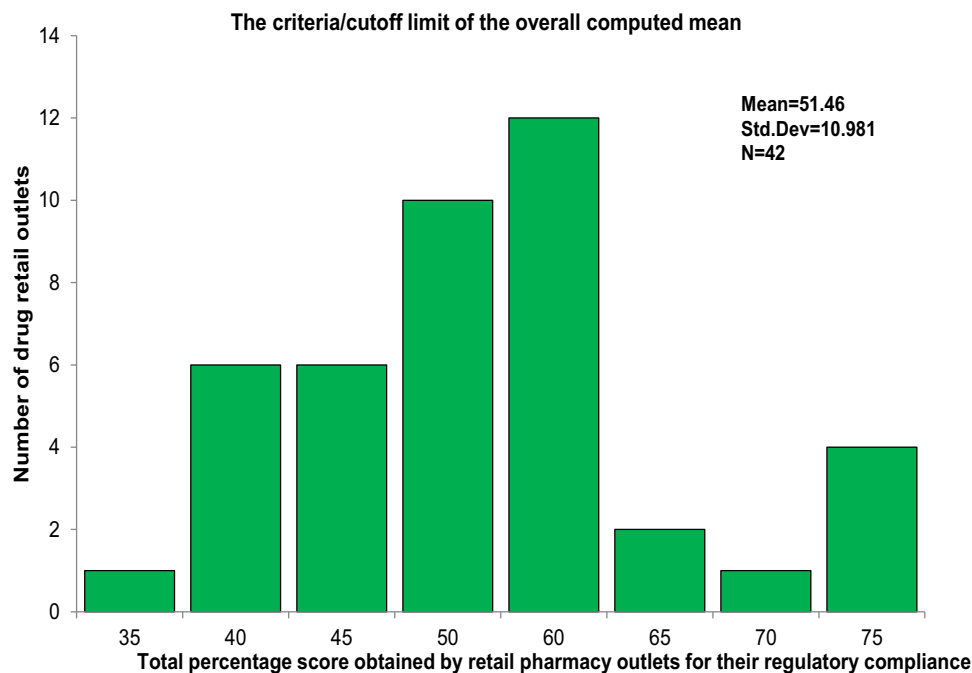


Figure 1 The criteria/cutoff limit of the overall computed mean.

Status of regulatory compliance of drug retail outlets

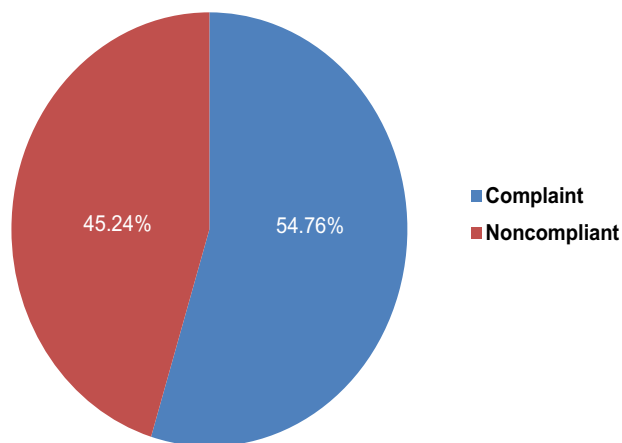


Figure 2 Status of regulatory compliance of drug retail outlets.

variance *t*-test revealed no significant difference between the mean of drug release samples at 60 min obtained from compliant and noncompliant drug retail outlets (p -value >0.05) (Table 4).

Discussion

While research findings confirm the existence of the private drug retail outlets that do not comply with regulatory standards in many low-income countries, there are a lack of reports that evaluates the quality of medicines from these retailers.^{11–18} Therefore, the quality amoxicillin

500 mg capsule samples were evaluated using the method mentioned in US Pharmacopeia after assessments of regulatory compliance of the drug retail outlets in Southwestern Ethiopia.

In this study, 42 private drug retail outlets of Jimma town were evaluated for regulatory compliance using the Ethiopian regulatory standard checklists. In addition, the quality of amoxicillin samples obtained from these retails were evaluated using methods described in the US Pharmacopeia. The present study revealed that about 54.76% of private drug retail outlets were compliant with the regulatory standard. Compared with studies conducted in Pakistan (19%)²⁵ and Tanzania (13%),²⁶ the current finding is higher regarding regulatory compliance of drug retail outlets. This difference may be related to variations of regulatory standards among given countries for licensing of retails and scope of methodologies that the authors employed to determine magnitude of compliance. The Fisher's exact test revealed that, types of ownership of the retail, income per month of the drug retail outlet, experience of dispenser, and training regarding good storage practice were associated with status of regulatory compliance of drug retail outlets. These imply that the professional dispenser, who owned the retail outlets, having more income per month, possessing adequate experiences and training regarding good storage practice may enhance regulatory compliance of private drug retails. Regarding quality of amoxicillin obtained from these retails, the physical characteristics of capsules,

Table 2 Association Between Independent Variable and Outcome Variables

Variables		Frequency	Compliance of Status of the Drug Retail Outlets		p-value
			Compliant	Noncompliant	
Owner of the drug retail outlet	Professional dispenser	26	18	8	0.026*
	Nonprofessional dispenser	16	5	11	
Service year of the drug retail outlets	<10 years	22	14	8	0.344
	>10 years	20	9	11	
Estimated income generation per month in Ethiopian Birr	<5000 Ethiopian birr	19	14	5	0.033*
	>5000 Ethiopian birr	23	9	14	
Status of the dispenser working in the drug retail outlets	Certified dispenser	39	22	17	0.581
	Noncertified dispenser	3	1	2	
Experience of dispenser	<10 years	22	16	6	0.029*
	>10 years	20	7	13	
Compliant regarding licensing requirements for drug retail outlets	Yes	12	4	8	0.098
	No	20	19	11	
Training regarding good storage practice?	Yes	18	6	12	0.028*
	No	24	17	7	

Note: *Statistically significant at p-value <0.05.

Table 3 Results of Quantity of API Capsules of Amoxicillin Samples (n=20) from Drug Retail Outlets

Parameters	Samples Obtained from Outlets that Complied to Regulatory Requirements			Samples Obtained from Outlets Did Not Comply to Regulatory Requirements		
	2021-004-001-C	2021-004-002-C	2021-004-003-C	2021-004-004-NC	2021-004-005- NC	2021-004-006- NC
Assay 1 (%c)	97.0	96.2	97.9	98.2	92.6	95.8
Assay 2 (%c)	97.3	96.1	98.0	97.8	93.0	95.7
Mean (%c)	97.2	96.1	97.9	98.0	92.8	95.7
Independent unequal variance t-test						
Mean of S1	97.2			98.0		
Mean of S2	96.1			92.8		
Mean of S3	97.9			95.7		

Notes: p-value >0.05. In sample codes C and NC indicate that sample is obtained from compliant and noncompliant drug retail outlets respectively; S1, S2, S3 are sample 1, sample 2, and sample 3, respectively.

packaging, and labeling information results obtained both from noncompliant and compliant retails revealed that all tested amoxicillin samples had no signs of moisture, dirty marks, embedded surface spots, and presence of empty capsules.

This indicates physical characteristics, packaging, and labeling of each 500 mg amoxicillin capsule samples were in

line with WHO guideline on packaging for pharmaceutical products.²⁴ Thus, the tested products may not have the stability problems associated with the packaging.²⁷ The identification test result indicated that none of samples from retails had incorrect active pharmaceutical ingredients (APIs). This shows that there is no risk of treatment failure or death due to the investigated products.²⁸ The assay result of APIs of the

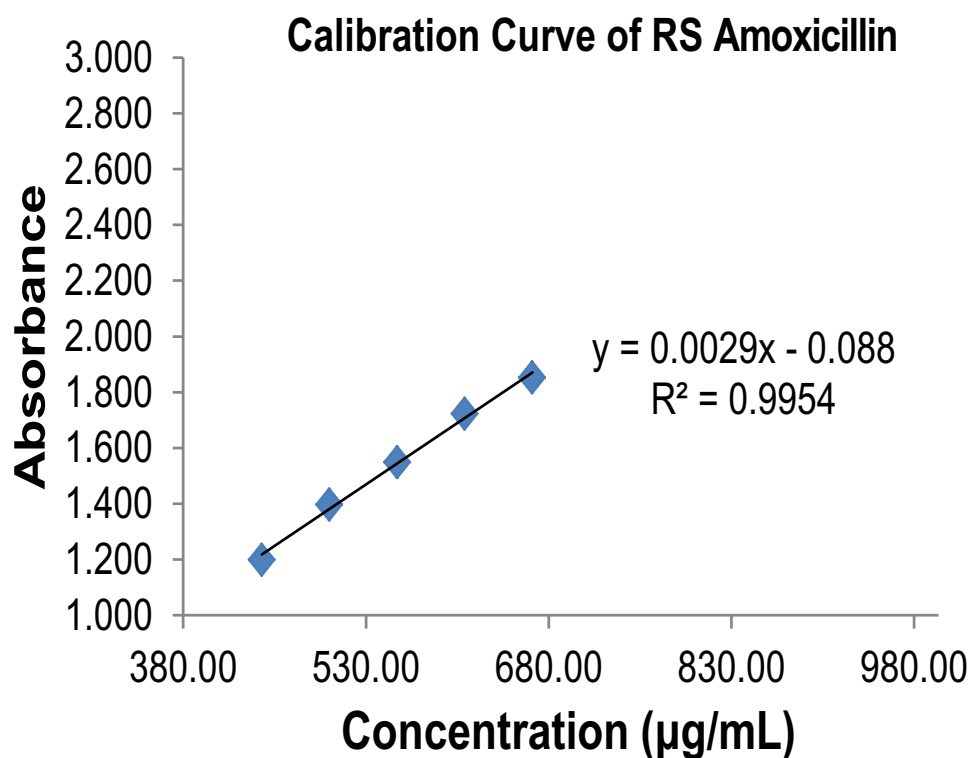


Figure 3 Calibration curve of amoxicillin reference standard in phosphate buffer at maximum wave length of 272 nm.

amoxicillin capsule samples obtained both from noncompliant (92.6% to 98%) and compliant (96.1% to 98.0%) retails complied with the Pharmacopoeia specification limit (% lc=90–120%).²³ The independent unequal variance *t*-test revealed that there is no significant difference between mean assay of API of the amoxicillin samples obtained from

noncompliant and compliant retails (*p*-value >0.05). Thus, the amount of APIs, the use of amoxicillin capsules obtained from noncompliant and compliant retails containing the same APIs may have similar clinical efficacy. However, the trend of variations of the assay results within and/or between noncompliant and compliant retails may potentially demonstrate the

Table 4 Cumulative Dissolution Data of Amoxicillin Release at 60 Minutes from the Samples Obtained from Selected Drug Retail Outlets Jimma, Ethiopia

Parameters	Samples Obtained from Outlets that Complied to Regulatory Requirements			Samples Obtained from Outlets Did Not Comply to Regulatory Requirements		
	2021-004-001-C	2021-004-002-C	2021-004-003-C	2021-004-004-NC	2021-004-005-NC	2021-004-006-NC
%DR1	104.04	97.92	99.14	96.08	99.75	98.53
%DR2	99.75	102.20	104.04	99.14	100.98	96.69
%DR3	101.59	99.75	100.37	99.75	102.82	97.92
Mean	101.80	99.96	101.18	98.32	101.18	97.71
Independent unequal variance <i>t</i> -test						
Mean of %DR of S1	101.80			98.32		
Mean of %DR of S2	99.96			101.18		
Mean of %DR of S3	101.18			97.71		

Notes: *p*-value >0.05. In sample codes C and NC indicates that sample is obtained from compliant and noncompliant drug retail outlets respectively. DR of S1, DR of S2, DR of S3 are drug release of percentage sample 1, sample 2, and sample 3, respectively.

impact of noncompliance of the retails on the quality of medicines. This finding is in line with the reports that have been suggested as the improper storage of drugs could result in degradation of APIs which are expected in noncompliant retailers.^{19,29–31} According to US Pharmacopeia the labeled amount of amoxicillin capsules dissolved for 60 min should not be less than 80% (NLT 80% (Q)). In this study, all tested samples compiled with Pharmacopoeia specification, and independent unequal variance *t*-test revealed no significant difference between mean of drug release samples at 60 min obtained from noncompliant and compliant retail outlets (*p*-value >0.05). This indicates that the use of Amoxicillin capsules obtained from noncompliant and compliant retails containing the same APIs may have similar bioavailability.

Conclusions

The regulatory compliance of private drug retail outlets in Jimma town is not satisfactory. Moreover, the laboratory findings revealed that all samples of amoxicillin capsules compiled with pharmacopoeial specification acceptance for packaging and labeling information, identification, assay, and dissolution. However, despite the fact that assays of the amoxicillin from both noncompliant and compliant retail outlets are within the required specification, the assays of amoxicillin obtained from noncompliant retailss appear to be slightly degraded which may potentially demonstrate the impact of noncompliance of the retails on the quality of medicines. Therefore, the investigators highly recommend the further research on comprehensive evaluation of many medicines to explore association between noncompliance and associated quality of medicines.

Abbreviations

APIs, active pharmaceutical ingredients; WHO, World Health Organization; RS, reference standard; USP, United State Pharmacopeia.

Data Sharing Statement

The documents supporting this study will be available upon request from corresponding author.

Ethical Approval and Consent to Participate

The Declaration of Helsinki was followed in undertaking this study. It was approved by the Institutional review board of Jimma University (Reference no. JHRPGD/921/20). A letter

of permission was received from the office of Jimma Regional Health Bureau. The informed consent of the study participants was taken prior to interviews for collection of data and evaluation of drug outlets. The withdrawal right of study participants from involvement of study at any time was assured.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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