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Research Article

Quality of Different Brands of Metronidazole Benzoate Oral Suspensions Availabe at Jimma Town, Southwest Ethiopia: Pharmaceuticals Quality Study

TeshomeSosengo[1]*, Fuad Adem[1], Jemal Abdela[1]
[1]School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Ethiopia
***Corresponding Author:** Teshome **Sosengo**, School of Pharmacy, College of Health and Medical Sciences, Haramaya University,Ethiopia.
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Abstract

Background: Poor quality drugs include substandard and counterfeit medicines. Poor quality antibiotics selectively kill the susceptible strain and leaves resistant strain to multiply. Metronidazole is a broad spectrum antibiotic whose effectiveness depends up on a dose administered to the patient.

Objective: The aim of the study is to assess the quality of different brands of metronidazole Benzoate oral suspension available in Jimma town, West Ethiopia.

Methods: Cross-sectional study was conducted in Jimma town, West Ethiopia from Feb 08 – Mar 28, 2018. The assay result of all the seven brands of Metronidazole Benzoate oral suspensions was entered to statistical package for social sciences software version 24.0 for windows. Then, one way analysis of variance was performed using Tukey test to determine whether there exists significant difference in assay result of the brands ($p<0.05$).

Result: All the seven Metronidazole benzoate oral suspensions assessed in this study passed British Pharmacopoeia 2013 specification of identity test of the drug. All the brands passed the assay test and total aerobic microbial count specification United States Pharmacopoeia 2015. The highest percentage of drug content was obtained for Metrolag, 105.56%, while the least content for Mizel, 93.12%. However, statistical comparison of drug contents at 95% confidence interval indicates that there is significant difference in drug content within and among the seven brands of Metronidazole benzoate oral suspensions ($p<0.05$). The pH of all the brands was with in United States Pharmacopoeia 2015 specification limit.

Key Words: Counterfeit, poor quality, specification, substandard drug

Introduction

Poor quality drugs include substandard and counterfeit medicines. Counterfeit drugs are drugs that deliberately/fraudulently misrepresent their identity, composition or source. Counterfeit drugs are deliberately/fraudulently misrepresent with their identity, composition or source [1, 2].

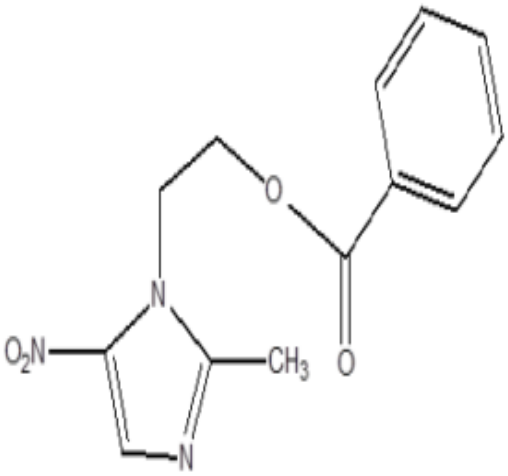
Poor quality pharmaceuticals invade health care system because of a number of problems starting from manufacture to final use by patients. Non-adherence to good practices in manufacturing, storage, distribution and dispensing, weak enforcement of pharmaceuticals regulatory laws, open borders, poor coordination of police and customs, corruption, double standards during production of pharmaceuticals i.e. better standards for manufacture of drugs to be exported rich countries and the poor standard for to be exported to poor countries as Sub-Saharan African countries and low educational level results in invasion of the health care system with poor quality pharmaceuticals [3, 4, 5,6, 7].

Poor quality drugs are common in countries with weak regulatory systems and hence the patients, government, the health care system and community in such countries are exposed to the deadly effects of the drugs [8, 9]. Pharmaceuticals regulatory system of Sub-Saharan African countries is weak [6]. In Ethiopia, there exists weak enforcement of regulations to control entry and distribution of pharmaceuticals, a factor that results in invasion of the pharmaceutical market by poor quality pharmaceuticals [10].

Good quality antibiotics kill the drug susceptible microbes, suppress multiplication of the drug resistant microbes, cure and/or halt progression of disease [11, 12, 13]. Poor quality antibiotics as substandard antibiotics selectively kill the susceptible strain and leaves resistant strain to multiply [14]. Micro-organisms that have developed resistance transmits resistance gene through exchange of genetic material [4]. An estimated 700,000 Africans die annually from consuming fake anti-malarial or tuberculosis drugs [13]. In Sub-Saharan Africa an estimated 400,000 children are exposed to malaria are treated with poor quality anti-malaria medicines [15].

Metronidazole is a broad spectrum antibiotic whose effectiveness depends up on a dose administered to the patient [16]. It is one of the commonly utilized antibiotic in Ethiopia [17, 18]. The chemical structure is shown below in figure 1.

To estimate the exact burden of poor quality medicines and formulate effective and efficient strategy to prevent exposure of the patient, community, government and the health care system from poor quality drugs and hence from its effects, there should plenty of data on status of poor quality drugs. To date, few data are available on poor quality drugs [1, 2, 19]. In Ethiopia, except a few attempt of certain scholars to assess quality of certain drugs circulating on the pharmaceutical market of the country, the quality status of Metronidazole benzoate oral suspensions marketed in pharmaceutical market yet remain unknown [20]. Therefore, this study assessed quality of different brands Metronidazole benzoate oral suspensions found in Jimma town.



Metronidazole benzoate

Figure 1: *Chemical metronidazole benzoate*

Methods and materials

Study area and period

The study was conducted in Jimma town, South west Ethiopia. It is located 350 km South West of Addis Ababa. The study was conducted from Feb 08 – Mar 28, 2018.

Study design

A cross sectional study was conducted to determine quality of metronidazole benzoate oral suspensions found in pharmaceutical market of Jimma town, South West Ethiopia.

Sample size determination

Enough samples, (i.e. each four bottles from each brand of metronidazole benzoate oral suspensions) that required to do post marketing quality control studies were purchased [21].

Sample collection technique

Samples were collected using convenience sampling technique [21, 22]. Detailed information of the samples purchased for analysis is indicated in tables 1.

Manufacturer	Brand Name	Strength	Batch Nº	Mfg.date	Exp.date
Neopharma, UAE	Metrolag	125mg/5ml	MZA16007	05/2016	05/2019
Unique Pharmaceuticals Labs., India	Metrogyl	125mg/5ml	ASX7001	Nov.2017	Oct.2019
Coral Laboratories Ltd., India	Cornizole	200mg/5ml	DCI1715	08/2017	07/2020
Julphar Pharmaceuticals Plc., Ethiopia	Negazole	125mg/5ml	0020	0/2017	09/2020
Fawes Pharmaceuticlas Plc., Ethiopia	Mizel	125mg/5ml	18005912	04/2018	04/2020
Cadila Pharmaceuticals Plc,India	Camezol	125mg/5ml	D17004BY37	Jul.2017	Jun.2020
Addis Pharmaceuticals Factory Plc.,Ethiopia	Metazol	125mg/5ml	24168	10/2017	10/2020

Table 1: *Detailed information on metronidazole benzoate oral suspension analyzed for quality.*

Quality Assurance

Sample collectors were trained for 2 day. Two sample collectors per a site were assigned for sample collection, one to purchase the drug and the other to handle and file the data of the purchased samples. The quality of data was checked by investigator. Next to the day of completion of sample collection, the samples was taken for laboratory analysis to EPHARM quality control laboratory in bag that protects the samples from direct sunlight and stored in conditions recommended on the respective the label claim of the brands in the EPHARM quality control laboratory sample storage section. All the chemicals and reagents used were of analytical grade and prequalified. The respective test result was carefully written and handled.

Data Analysis

The quality of the samples were assessed based up on a method specified in BP 2013 and USP 2015 and the test results were compared with respective official specifications of BP, 2013 and USP, 2015. The assay result of all the seven brands of metronidazole benzoate oral suspensions was entered to statistical package for social sciences software version 24.0 for windows. Then, one way analysis of variance (ANOVA) was performed using Tukey test to determine whether there exists significant difference in assay test results within and among the brands ($p<0.05$).

Ethical Approval

The study was reviewed and approved by the ethical review committee of Jimma University, Institute of Health Sciences**.**

Operational definitions

Counterfeit drugs: Drugs that deliberately/fraudulently misrepresent their identity, composition or source.

Good dispensing practice: Delivery of the correct medicine to the right patient, in the required dosage and quantities with clear medicine information counseling and appropriate follow up.

Good distribution practice: Distribution of pharmaceuticals according to the principles of GMP and good storage practice (GSP) that maintains the stability of the drug thought its shelf life.

GMP: Manufacturing practice that enables the manufacture of pharmaceutical products continuously and consistently in quality standard appropriate for intended.

Quality: The degree to which a set of inherent properties of a product, system or process fulfills requirements.

Poor quality drugs: Drugs that include substandard and counterfeit medicines.

Total aerobic microbial count (TAMC) test: A test used to detect and estimates Staphylococcus aureus, Pseudomanas aerugnosa, Bacilus subtilis and Candida albicans.

Substandard drugs: Substandard drugs are genuine drugs that fail to meet either quality standards or specifications or both.

Materials Equipment's

FTIR 8400S (SHIMADZU, Japan), HPLC(Japan), UV-Spectrophotometer(Shmadzu/Japan), evaporating dish(Britain), sonicator(Bandelin/Germany), thermometer(Frankfurt/Germany), volumetric flask(England), pycnometer(Germany), Whatman GFC paper(England), conical flask(MERK /Germany), 0.45µm Nylon membrane filter(Germany), analytical balance(METLER TOLEDO, Switzerland), pH(Metler Toledo, China), incubator (SANYO, Japan), heating oven(Eclipse, Italy), and KBr(Britain).

Solvents/Chemicals/Reagents

Methanol(CARLOERBA/France), glacial acetic acid(CARLOERBA/France), acetontile(India), monobasic potassium phosphate(CARLOERBA/France), thioglycolate medium(Himedia laboratory Pvt.Ltd/India), IPA(National Alcohol/Ethiopia), acetone(CARLOERBA/France), TSA(Sisco reasercher Laboratory/India), distilled water(EPHARM/Ethiopia). Metronidazole benzoate BP RS (lot no. MBO/15120558 with potency of 99.9 %) was obtained from EFMHACA.

Tests Identification test

First, 10 mg of metronidazole benzoate reference standard (RS) was placed on Potassium Bromide (KBr) plate and taken to the fourier transform infrared spectroscopy (FTIR) instrument and its IR absorption spectrum was measured in a wave number range of 400cm^{-1} to 4000 cm^{-1}. Then, 10mg of metronidazole sample was taken with KBr plate to IR instrument and its IR absorption spectrum was measured in a wave number range of 400cm^{-1} to 4000 cm^{-1} (23).

Assay test

Three replicate 5µl sample solutions were injected automatically to the HPLC. Then, the percentage of the labeled amount of metronidazole benzoate in the brands was calculated (24).

Total aerobic microbial count (TAMC) test

First, all the seven brands of metronidazole benzoate oral suspension was visually checked for any irregularity and stored at room temperature. Then, sample number was assigned to the brands based on their expiry. The outer surfaces of bottles were cleansed with 70% isopropyl alcohol and placed in laminar air flow room and allowed to air dry. The exterior of each bottle was disinfected with 70% Isopropyl alcohol and shacked to maximize microbial dispersment and transferred to clean room. Then, each unit container was aseptically opened in a controlled (i.e. clean) room and 1ml of the sample was mixed with 10ml of distilled water and filtered through 0.45µm membrane filter. The membrane filter was rinsed with five 10ml of distilled water. Finally, 100 ml of tryptone soya agar was transferred to the membrane filter and incubated at 32°C for 3days [24].

Specific gravity test

First, pycnometer was cleaned and dried. Then, the tare weight of the pycnometer was determined by weighing it in balance. Then, the pycnometer was filled with water. Then, the weight of water was determined by subtracting the weight of empty pycnometer from the weight of water filled pycnometer. Then, the pycnometer was filled with the samples and the respective weight of the sample filled pycnometer was determined. Then, the weight of each sample was determined by subtracting the tare weight of the pycnometer from respective weight of sample filled pycnometer. Finally, the specific gravity of each sample was obtained by dividing the weight of sample by weight of water.

pH test

First, the pH sensor was rinsed with water and then with a few portions of the sample. Then, the pH sensor was immersed in to the test sample and sufficient time was allowed for stabilization of the pH measurement. Then, pH value was recorded for each sample.

Result and Discussion

Identification test result

The identification test for the seven brands of Metronidazole benzoate oral suspensions was performed according to a method indicated in BP 2013 for identification of the drug. The FTIR spectrum of the Metronidazole benzoate reference standard and the study samples is coinciding **(Figure 2**). As indicated on the figure, all the seven brands passed the test BP 2013 identification test specification for the drug. In contrary to this study result, identification study failure was reported in study done in America [25].

Active pharmaceutical ingredient void pseudo-pharmaceuticals can overflow in the pharmaceutical market of developing like Ethiopia at any time because of prevalence of predisposing factors in the countries like open border, poor co-ordination of police and law enforcement agencies, non-adherence to good manufacturing practice, counterfeiting and corruption. There should be strict control to avoid prevalence of active pharmaceutical ingredient void pseudo-pharmaceuticals in pharmaceutical market of developing countries.

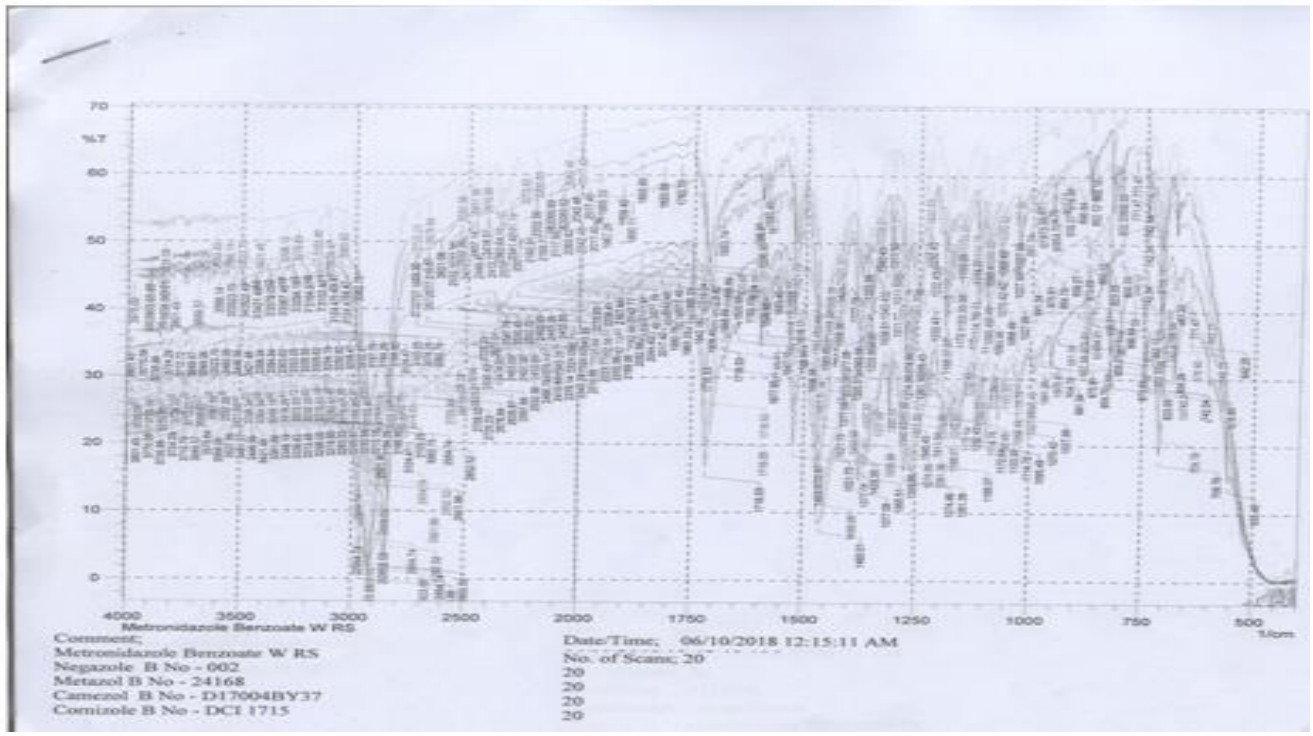


Figure 2: *Merged FTIR spectrum of Metronidaole Benzoate RS and the study samples*

Assay of metronidazole benzoate oral suspensions: All brands of metronidazole benzoate oral suspension passed the test for assay of active pharmaceutical ingredients as per USP 2015 specification. The highest percentage of drug content was obtained for metrolag, 105.56%, while the least content for mizel, 93.12% (**Table 2**). Similar to study result with regard to assay(i.e. content of API) , all brands of metronidazole studied passed assay test in studies done at pakistane in Peshwar and Karachi, Pakistan [26, 27]. However, statistical comparison of drug contents at 95% confidence interval indicates that there is significant difference in drug content within and among the seven brands of Metronidazole benzoate oral suspensions ($p<0.05$). In opposite to this study finding, failure to comply for assay test was reported in study done in Mongolia (28). The cause for the product to fail assay test on the study may be non-compliance to good practices starting from manufacture to distribution and storage of the products [3, 6].

Non-adherence to good manufacturing, distribution, storage and dispensing practices results availability of substandard (drugs that contain active pharmaceutical ingredient below specified therapeutic dose) quality drugs in pharmaceutical market of developing countries. Developing countries should strictly control such malpractices through harmonization for medicines regulation with drug regulatory authorities of their neighboring and/or developed countries.Table 2: Assay result of Metronidazole capsules and Metronidazole injections (n=3).

Product	Brand Name	Assay Result (%)	±RSD (%)	USP 2015 limit
Metonidazole benzoate suspension	Camezol	102.06	0.102	90-110%
	Cornizole	101.23	0.233	90-110%
	Metazol	93.94	0.042	90-110%
	Metrolag	105.56	0.05	90-110%
	Metrogyl	104	0.110	90-110%
	Mizel	93.12	0.089	90-110%
	Negazole	101.7	0.051	90-110%

Microbiological quality test

Total aerobic microbial count (TAMC) test

The suspensions were tested for total aerobic microbial count according to a method specified in USP 2015. Non-sterile pharmaceutical products total aerobic microbial count should be less than 1000 cfu/ml after 3-5 days of incubation in the tryptone soya agar (TSA) culture. Thus, all the seven brands of metronidazole benzoate suspension analyzed passed. The microbiological quality assessment result of the current study is better than microbiological quality assessment study results of studies done in South Eastern Nigeria [29], Dar Es Salaam, Tanzania [30] and Sri Lanka [31], where 4 from 17 brands of suspensions (1 from 8 metronidazole suspensions and 3 from 9 brands of co-trimoxazole suspensions), 3 brands of water for injection from 27 brands (24 brands of quinine sulphate and 3 brands of water for injection) and 1 sample(lactulose suspension) from five samples(samples of lactulose, cephalexin, amoxicillin, paracetamole and salbutamole suspensions) was found to be microbiologically contaminated. The cause for the samples to fail microbiological quality tests may be non-adherence to good storage and transport practice during the storage and transport of the products. The results of total aerobic microbial count (TAMC) of the study samples and its negative control are shown below (**Table 3 and 4**).

Microbiological spoilage of suspension dosages forms results in instability of the formulation as flocculation, color change and degradation of the excipient and APITable 3: Total aerobic microbial count (TAMC) test result of metronidazole benzoate oral suspensions (n=1).

Brand name	TAMC (cfu/ml)	Limit
Camezol	20	<1000 cfu/ml
Cornizole	10	<1000 cfu/ml
Metazol	<10	<1000 cfu/ml
Metrogyl	20	<1000 cfu/ml
Metrolag	10	<1000 cfu/ml
Mizel	<10	<1000 cfu/ml
Negazol_	<10	<1000 cfu/ml

Table 4: *Metronidazole benzoate oral suspensions total aerobic microbial count (TAMC) test negative control test result (n=1).*

Negative control	Result
100 ml Trypton soya agar	-ve

Specific gravity test

For suspensions to have good dispersion of the ingredients, the specific gravity of the suspension should be around one. All metronidazole benzoate oral suspensions have a specific gravity value more than one which could cause sedimentation of the ingredients suspension which results in instability and uneven distribution of the API of the suspension (**Table 5**)

pH test

The pH of all the brands of metronidazole suspensions analyzed in the present study is within a tolerance range of BP 2013 (**Table 6**). For metronidazole suspensions to be stable and hence to be therapeutically effective, its pH should remain in the specified shelf life.Table 5: Specific gravity test result of metronidazole benzoate oral suspensions

Brand name	Total weight	Weight of the sample	Specific gravity
Camezol	24.7787	13.1418	1.1744
Cornizole	25.3586	13.7217	1.2263
Metazol	24.8812	13.2443	1.1836
Metrolag	24.9294	13.2925	1.1879
Metrogyl	25.8062	14.1698	1.2663
Mizel	25.1408	13.4539	1.2023
Negazole	25.1206	13.4837	1.2050

Table 6: *pH test result of metronidazole benzoate oral suspensions (n=3).*

Brand name	pH value	BP 2013 range
Camezol	5.50	5-6.5
Cornizole	5.29	5-6.5
Metazol	5.6	5-6.5
Metrogyl	5.43	5-6.5
Metrolag	5.91	5-6.5
Mizel	5.86	5-6.5
Negazole	6.05	5-6.5

Conclusion:

In the present study all the seven brands of Metronidazole benzoate oral suspensions assessed for quality passed all conventional quality assessment studies indicated in Pharmacopoeia. However, there exists significant difference within and among assay test result of the brands. Poor quality drug can be imported to the developing countries at any time, may be because of poor co-ordination of police and custom, open borders and other reasons such as corruption and causes deleterious impacts on patient, community, health care system and the government. Therefore, post marketing quality assessment studies should be performed regularly to determine quality status of the drug on market and take appropriate action to prevent incidence of poor quality medicines.

Limitation of the study

The present quality assessment study result may not indicate the quality status of the drug throughout Jimma town or the country Ethiopia, for samples analyzed in this study were collected by convenience sampling.

Acknowledgement

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Declarations

Consent to publish: Not applicable

Funding: Jimma University

Competing interests: The author declare no competing interest.

Conflict of Interest: The authors declare no conflict of interest

Author's contribution

Author Teshome Sosengo involved in the conception and design of the study, participated in the literature searches, supervised data collection and analyzed data. Author Jemal Abdella involved in the conception and design of the study, participated in the literature searches, analyzed data and wrote the manuscript. All the authors approved the final manuscript.

Availability of data

All the primary are available with the corresponding author, Teshome Sosengo

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