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COMPARATIVE QUALITY EVALUATION OF SOME METRONIDAZOLE TABLETS AND METRONIDAZOLE BENZOATE ORAL SUSPENSIONS AVAILABLE IN RETAIL OUTLETS OF ADDIS ABABA, ETHIOPIA

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ABSTRACT: In this study, five different products of each metronidazole tablets and benzoate salt oral suspensions were purchased from the different retail outlets in the local market of Addis Ababa and analyzed using official methods (Pharmacopoeial methods of USP/BP/IP) by employing HPLC for the tablet dosage forms and non-aqueous titration with potentiometric end point for the suspensions. The assay results showed that all brand and generic products of metronidazole tablets and metronidazole benzoate oral suspensions met the USP and the IP specifications, respectively. Furthermore, all the tablets analyzed have passed the hardness, friability and weight variation tests. All tablets except metrogyl passed the disintegration time test and dissolution rate test specifications of BP/USP. In addition, different brands and a generic product of metronidazole benzoate oral suspensions were evaluated by determining their physical stability with respect to the two useful parameters, sedimentation volume and Viscosity. Amrizole has relatively moderate viscosity (728.0 ± 0.12 cP), which may cause good pourability of the suspension with a sedimentation value of 1 (acceptable and stable suspension). On the other hand Camezol has low viscosity (9.2 ± 0.40 cP) and sedimentation Value (0.10) that may cause faster sedimentation of the particles of the suspension. This study showed the importance of post marketing surveillance for the drugs imported and distributed in the country, Ethiopia.

INTRODUCTION: Metronidazole is a nitro-imidazole derivative that has been synthesized in various laboratories throughout the world [1].

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It was introduced as an antiprotozoal agent, but it is also active against anaerobic bacteria [2]. Metronidazole is chemically (2-(2-methyl-5-nitro-1*H*-imidazol-1-yl) ethanol). Metronidazole Benzoate is chemically (2-(2-methyl-5-nitro-imidazol-1-yl) ethyl benzoate) [3].

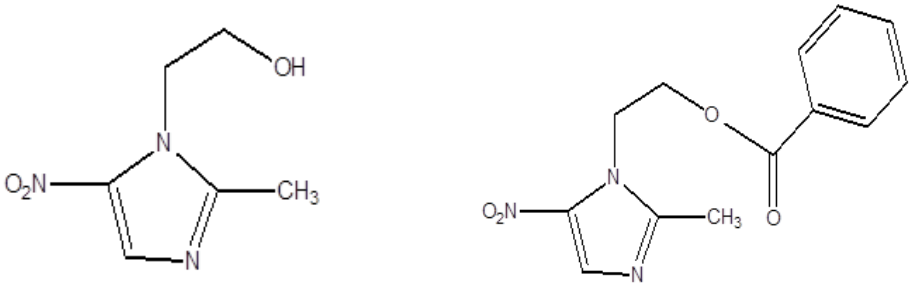
The chemical structures are shown in **Figure 1**. Metronidazole benzoate is prepared as a suspension form which is indicated in the treatment of infections caused by a wide range of anaerobic bacteria, protozoa and bacteroides [4, 5].

A suspension of metronidazole benzoate is often substituted for metronidazole in pediatric oral preparations because of the bland taste of the ester compared to the bitter taste of the free base [3].

The main purpose of an oral tablet and suspension is to deliver a certain and defined amount of drug to the human body through GI system. Studies on bioavailability of drugs from different manufacturers showed that in many situations tablets and suspensions with same drug and drug content did not give the same therapeutic response. Formulation additives in the tablet, physical form of the drug used in the tablet and manufacturing process variation from manufacturer to manufacturer are responsible for the variations observed in the dissolution profile and therapeutic effect [6]. Poor quality medicines do not meet official standards for strength, quality, purity, packaging and labeling. Use of counterfeit and substandard drugs bears serious health implication; such as treatment failure, adverse reactions, drug resistance, increased morbidity and mortality. In combating such type of problems studies on quality assurance must be carried [7].

Thus, the main objective of this study was to assess the quality of metronidazole tablets and metronidazole benzoate suspensions of different brands and generic products available in the market.

In this study, Metronidazole tablets which are available in 500 mg and 250 mg doses as well as Metronidazole benzoate suspensions formulated in 5 mg/100 ml and 5 mg/120ml strengths were purchased from the market. All the available products were included in the assessment. The physicochemical parameters weight variation, hardness, friability, disintegration time, dissolution rate, identification test of the tablets, sedimentation volume and viscosity for oral suspension and assay for both tablets and oral suspensions were considered during the present study.



(A) METRONIDAZOLE **(B) METRONIDAZOLE BENZOATE**

FIGURE 1: CHEMICAL STRUCTURES OF METRONIDAZOLE (A) AND METRONIDAZOLE BENZOATE (B)

MATERIALS AND METHODS [8-11]:

Instrumentation: For the analysis of metronidazole content in their dosage form High performance liquid chromatography (Total Chrom work station, Perkin Elmer series 200 Diode Array detector, UV-Visible detector, pump, auto sampler, vacuum degasser, Perkin Elmer Network Chromatography Interface (NCI) 900, Perkin Elmer Instrunments, Norwalk, CT 06859 USA), HPLC column (4.6-mm x 15-cm column that contains packing octylsilane chemically bonded to totally porous silica particles, 5 to 10 micrometer in diameter,) and double beam UV-Visible spectrophotometer (Unicam, England) were used.

For the analysis of physical properties of metronidazole tablet and metronidazole benzoate oral suspension; Friability tester (SOTAX®, F_2 Friabilator USP, Switzerland), Integrated hardness, thickness and diameter tester (Pharma Test®, PT^B 311, Germany), disintegration apparatus (ERWEKA, ZT 3, Germany), dissolution apparatus (ERWEKA, DT 700 HH, Germany), Rotational Viscometer, L_3 spindle, 10 ml measuring cylinder and beakers were used.

Materials & Reagents: The chemical substances that were used in this study were HPLC grade These include methanol, hydrochloric acid, acetic anhydride, Glacial acetic acid, potassium biphthalate, perchloric acid, chloroform, acetone. Metronidazole reference standard (International chemical reference substance, ICRS, control No. 183118., WHO center for chemical reference substances Solna 3, Sweden) was obtained from Ethiopian Pharmaceutical Manufacturing Share Company (EPHARM), Cellulose nitrate filters (pore size 0.45 μm, Sartorius Germany) were used for filteration purpose.

Metronidazole Tablet and Suspension Samples: The different brands and generic products of metronidazole tablets and metronidazole benzoate oral suspensions were obtained from retail pharmacies in Addis Ababa and the details are described in **Table 1 (a and b)** and all the products were within their shelf life at the time of the study.

TABLE 1: METRONIDAZOLE SAMPLES USED IN THE STUDY

A. TABLETS

S. No.	Manufacturer	Brand name	Package	Batch number	Manufacturing date	Expiry date
1	SB, India	Metazole (500mg)	Blister	3018	*	09/2006
2	Unique pharmaceutical laboratories, India	Metrogyl (250mg)	Blister	U4001A	Sep, 2003	09/2006
3	Amrya pharma, Egypt	Amrizole (250mg)	Blister	901111	07/2005	07/2009
4	Lagap, Switzerland	Metrolag (250 mg)	Blister	6978	05/2005	05/2010
5	Shijazhuang, China (supplied by Mision pharma, Denmark)	Metronidazole (Generic) (250 mg)	Hospital pack (tin)	04/0601	06/2004	06/2007

B. SUSPENSIONS

S. No.	Manufacturer	Brand Name	Package	Batch Number	Manufacturing date	Expiry date
1	Lagap, Switzerland	Metrolag	Bottle 100ml	MZA 4007	09/2004	08/2007
2	Amrya pharma, Egypt	Amrizole	Bottle 120 ml	951228	07/2005	07/2009
3	IPCA Laboratories, India	Giardyl-125	Bottle 100ml	AKW 5001R	Jul, 2005	Jun, 2008
4	Flamingo, India	Metronidazde (Generic name)	Bottle 120 ml	109	07/2005	06/2008
5	Cadila, India	Camezol	Bottle 100ml	E5005	05/2005	04/2008

Methods:

1. **Identification Test:** The identification test for metronidazole tablet and metronidazole benzoate oral suspension was done with the method specified in USP XXVII and Indian Pharmacopoeia respectively.

2. **Uniformity of weight:** 20 tablets were selected at random and weighed individually as well as the average weight of tablets was determined. Then the percent of weight variation is calculated.

3. **Hardness Test**: The hardness of each tablet was determined using Hardness Tester by selecting ten tablets randomly. Each tablet was placed between two anvils and force was applied to the anvils. The crushing strength that just causes the tablet to break was recorded. Crushing strength of average ten tablets was recorded.

4. **Friability:** In the friability testing, twenty tablets of known weight (de-dusted before) from each product were placed in the friability tester and were subjected to combined effects of abrasion and shock by placing them in a plastic chamber that revolves at 25 rpm for 4 min. The tablets were then sieved and weighed. The percent loss in weight was calculated as friability

5. **Disintegration Time Test:** Disintegration time test was carried out according to USP/NF specification (USP XXVII)[8]. Six tablets were placed in a disintegration tester filled with distilled water at 37 ± 0.5^0C. The disintegration time of each tablet was determined and the average disintegration time was calculated.

6. **Dissolution Rate Test:** The dissolution rate test was carried out in USP type-I dissolution apparatus and the apparatus was operated at 100 rpm for 60 min. The specimens were withdrawn at 10, 15, and 20, 30, 40, 50 and 60 minutes and were analyzed by UV at 274 nm using 0.1N hydrochloric acid as blank.

7. **Sedimentation Volume:** The studied suspensions were stored in different measuring cylinders (10 ml) for 48 hours and the height of sediment in each cylinder was recorded. The sedimentation volume was calculated

8. **Viscosity:** Sufficient amount of suspensions were transferred to a beaker and the viscosity measured. The spindle of the viscometer was rotated at 100 rpm at a temperature of 21^0 C.

Assay:

Assay of Metronidazole Tablets: 10 metronidazole tablets were weighed and finely powdered and average weight of powder equivalent to 1gm was taken and dissolved in about 50 ml of methanol and sonicated to dissolve. It was diluted with methanol to 100 ml and 5.0 ml of the clear supernatant liquid was pipetted and diluted to 100 ml. About 20 µl of the working reference standard and sample preparation were injected automatically to the HPLC. The quantity was calculated, in mg/ml of metronidazole.

Assay of Metronidazole Benzoate Oral Suspension: The assay was carried out according to Indian Pharmacopoeia. A quantity equivalent to 200 mg of metronidazole was measured accurately; 10 ml of water was added and extracted with 25 ml of chloroform four times. The chloroform extracts were combined and washed with 5 ml of water twice. The aqueous solution was then washed with 5ml of chloroform and the combined extracts and washings were evaporated to dryness on a water-bath.

Two successive quantities each of 25 ml of acetone were added and then 10 ml of acetic anhydride was added. The resulting solution was titrated using 0.1M perchloric acid and the equivalence point was determined potentiometrically.

RESULTS AND DISCUSSION: The identification tests of all drugs showed positive results as per the specifications of USP/NF [8], BP [9] and IP [10]. The metronidazole tablets (brand and generic) HPLC retention time of the major peaks corresponded to that of the reference standard preparation, as obtained in the assay as shown in **Table 2**. The residue of the extract of metronidazole benzoate oral suspension 0.001% w/v solution in ethanol has exhibited a maximum light absorbance at about 309 nm, about 30mg, which comply with the IP specification. The residues of the extract have also melted at 100^0 c as specified in IP of method I. The identification result of metronidazole benzoate oral suspensions is presented in **Table 3**.

TABLE 2: RESULT FOR THE UV ABSORPTION AND HPLC RETENTION TIME OF METRONIDAZOLE OBTAINED FROM STUDIED TABLETS

Product	Wave length of Maximum Absorption (nm)		Retention time (min.)
Metazole	278	242	4.80
Metrolag	278	242	4.80
Amrizole	278	242	4.80
Metronidazole (generic)	278	242	4.80
Metrogyl	277	242	4.80

TABLE 3: UV ABSORPTION WAVE LENGTH AND MELTING POINT OF METRONIDAZOLE BENZOATE OBTAINED FROM THE STUDIED ORAL SUSPENSIONS

Product	Wavelength of Maximum Absorption (nm)	Melting point (^{o}C)
Giardyl	310	99.0
Metrolag	310	99.5
Amrizole	310	100.0
Metronidazole (generic)	310	101.0
Camezol	310	100.5

All the brands and generics exhibited good hardness strength (greater than 50 N), which is required for safe handling and transportation. The result shows that there is large difference in crushing strength of the products. Amrizole (150.97 ± 26.37), and metazole (121.04 ± 14.35) have very high crushing strength. Metrogyl (60.95 ± 3.84), metronidazole (generic) (58.44 ± 6.7), metrolag (55.40 ± 8.46) have relatively lower crushing strength. The average hardness and disintegration time test results of the different tablets of metronidazole included in the study are presented in **Table 4**.

TABLE 4: RESULTS OF HARDNESS & DISINTEGRATION TIME TEST OF STUDIED METRONIDAZOLE TABLETS

Product	Hardness (N) ± SD	Mean disintegration time (Min.)±SD
Metazole	121.04±14.35	2.5±0.44
Metrolag	55.40±8.46	2.5±0.44
Amrizole	150.97±26.37	7.02±0.35
Metronidazole (generic)	58.44±6.7	5.97±0.10
Metrogyl	60.95±3.84	Did not disintegrate

USP [8] and BP [9] state that tablets should disintegrate within the prescribed period of time. All metronidazole tablets except metrogyl (film-coated tablet) disintegrated in less than 15 minutes, which is recommended in BP for uncoated tablets. Metrogyl is a film-coated tablet, which had different disintegration specifications in BP from uncoated tablets. The recommended disintegration time for film-coated tablets in BP is within 30 minutes. But metrogyl failed to comply with this specification which was also reflected by the dissolution rate test. It is known that the type of binder used will affect the disintegration time of a tablet. Although metazole has large crushing strength (121.04±14.35), the disintegration time is very short indicating proper optimization of the formulation. The crushing strength of metrogyl (60.95±3.84) is small but it was not disintegrated within the specified time (suggesting use of inappropriate binder). Loss of less than 1% of the weight of tablets after friability or abrasion tests is generally considered acceptable. The results of friability test are presented in **Table 5**. This shows that the friability of the uncoated tablets was found within limits specified in the USP/NF suggesting the use of appropriate binder. The content of Metronidazole in each tablet brand was within the limits prescribed by the U.S.P [8]. The average weight of tablets is presented in Table 5. All the tablets passed the weight variation test.

TABLE 5: RESULTS OF FRIABILITY TEST AND WEIGHT VARIATION OF THE STUDIED METRONIDAZOLE NON-COATED TABLETS

Product	Weight (g) before test	Weight (g) after test	% Loss	Average weight (±SD)
Metazole	11.903	11.901	0.051	598.03 ± 7.61
Metrolag	9.023	9.000	0.25	452.4 ± 7.57
Amrizole	10.031	10.030	0.009	501.04 ± 3.26
Metronidazole	6.710	6.677	0.49	329.84 ± 4.52
Metrogyl (film-coated)	-	-	-	348.12 ± 3.36

According to BP [9], if the tablets are uniform in weight, it is likely that the tablets will be uniform in drug content also. Hence, the BP specifies that no more than two of the individual weights deviate from the average weight by more than 5% deviation and none should deviate by more than 10%. The individual weights of metronidazole tablets were within the Pharmacopoeial specification and hence all products passed dosage unit uniformity requirements.

An oral suspension is more acceptable and stable when the sedimentation value approaches to one [12]. However, only one product (amrizole) has a sedimentation value of 1 while other products have a sedimentation value of less than one. In the present study, metronidazole benzoate (generic) has relatively higher viscosity (1194.0 cP), which may cause difficulty to take accurate dose since higher viscosity affects pourability of the suspension. On the other hand Camezol has low viscosity that may cause faster sedimentation of the particles of the suspension. Amrizole has relatively moderate viscosity that may be easy to pour from the container. Results of sedimentation volume and average viscosity are presented in **Table 6**.

All metronidazole tablets passed the dissolution test as prescribed by U.S.P except one brand (metrogyl). The dissolution rate test result is in line with the disintegration time test of the products in which all the tablets except metrolag shows immediate disintegration. Statistically when the result is compared at 20 minutes, with 95% confidence interval, metrogyl is completely different from other products ($P < 0.001$) while other products didn't show any significant difference ($P > 0.05$).

Thus metrogyl showed different *in vitro* drug release, which may also exist in its *in vivo* test, affecting bioavailability. This suggests the problem of bioequivalence. The combined time dependent drug release profile of all metronidazole products is illustrated in **Table 7** and **Figure 2**.

TABLE 6: RESULT OF SEDIMENTATION VOLUME AND VISCOSITY MEASUREMENT OF THE STUDIED METRONIDAZOLE BENZOATE ORAL SUSPENSIONS

Product	Total volume of Suspension (ml)	Volume of Sediment (ml)	Sedimentation Volume	Average Viscosity (cP)*± SD
Metronidazole benzoate/Generic/	10	5.4	0.54	1194.0 ± 0.23
Camezol	10	1.0	0.10	9.2 ± 0.40
Amrizole	10	10.0	1.00	728.0 ± 0.12
Metrolag	10	3.6	0.36	174.6 ± 0.24
Giardyl	10	3.4	0.34	332.0 ± 0.63

TABLE 7: RESULTS OF TIME DEPENDENT DRUG RELEASES OF STUDIED METRONIDAZOLE TABLETS

Time of sampling (min)	Percent of drug released (W/W)				
	Metrogyl	Metronidazole (generic)	Amrizole	Metrolag	Metazole
10	13.16	96.01	88.44	97.72	70.32
20	30.82	98.35	98.00	99.36	97.82
30	42.00	99.00	100.00	99.36	98.37
40	51.60	99.25	99.97	100.00	99.00
50	59.76	98.20	100.00	100.00	98.18
60	66.87	99.27	100.00	98.41	98.00

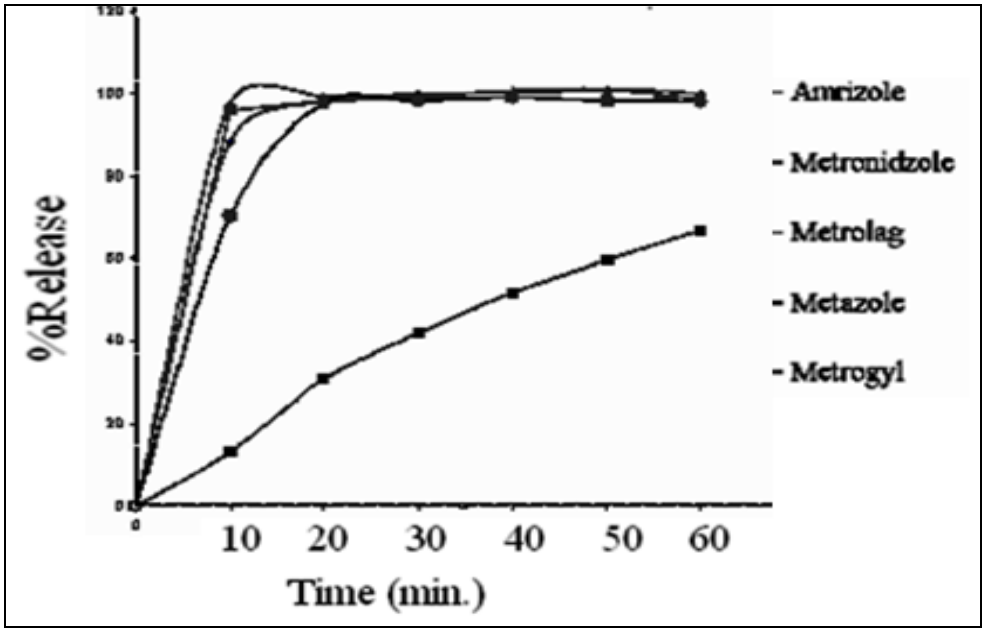


FIG. 2: TIME DEPENDENT DISSOLUTION PROFILE OF DIFFERENT BRANDS AND GENERIC PRODUCTS OF METRONIDAZOLE TABLETS

Chemical assay of each drug used in the study was done using official methods in the specific monographs. Metronidazole tablets were analyzed by using USP, methods, which specify that tablets should contain not less than 90.0 and not more than 110.0 percent of the labeled amount. Metronidazole benzoate oral suspensions were analyzed using specifications in Indian pharmacopoeia (IP) and it should contain not less than 90.0 and not more than 110.0 percent the labeled amount. The assay results are given in **Table 8**.

Assay results showed that all brands and generic products of metronidazole tablets (according to U.S.P) and metronidazole benzoate (according to Indian Pharmacopoeia, IP) oral suspensions were within pharmacopoeial limits. The statistical results of the assay of tablets showed that there is no significant difference between all products ($P>0.05$). As presented in Table 8 all products of metronidazole benzoate oral suspensions showed assay results within the pharmacopoeial limit.

TABLE 8: ASSAY RESULT OF STUDIED METRONIDAZOLE TABLETS AND METRONIDAZOLE BENZOATE ORAL SUSPENSIONS

Drug formulation	Products	Assay results (%w/w) ± RSD
Metronidazole tablets	Metazole	96.2 ± 3.80
	Metrolag	94.23 ± 0.67
	Amrizole	97.11 ± 2.80
	Metronidazole /Generic/	99.87 ± 1.28
	Metrogyl	99.87 ± 1.28
Metronidazole benzoate oral suspensions	Metronidazole benzoate /Generic/	97.57 ± 1.9
	Camezol	102.02 ± 0.0
	Amrizole	99.33 ± 1.2
	Metrolag	100.34 ± 1.39
	Giardyl	102.14 ± 1.95

Similar comparison studies of metronidaole preparations in other parts of the world demonstrate mixed results in *in-vitro* evaluation. A study of different brands of metronidazole tablets in Eastern Nigeria report significant variations among brands in some in vitro characteristics to the extent failing to fulfill pharmacopoeial requirements [13]. But the other study in Bangladesh of 40 metronidazole products (30 tablets and 10 suspensions) showed good quality results where only 4 tablets and 2 suspensions failed the potency test [14].

Besides, most bioequivalent *in- vivo* studies of metronidazole tablets in Nigeria [15], Metronidazole suspensions in Egypt [16] and metronidazole tablets in Iran [17] demonstrated the bioequivalency of the investigated products in comparison with the innovator ones. Because of such and other positive bioequivalent results in *in-vivo* studies, metronidazole tablets are suggested to be classified in the biowaiver class to the biopharmaceutics classification system of class I for immediate oral release solid oral dosage forms. [18]. Here results in our in vitro dissolution studies also support the immediate release of the active ingredient in the tablets except for one brand which is film coated in which the coating might interfere in its disintegration and dissolution properties of the product.

CONCLUSION: In this study, an attempt has been made to evaluate the physical and chemical properties of different brands and generic products of metronidazole tablets and metronidazole benzoate oral suspension. The physical properties of tablets such as hardness, friability, and disintegration time of the products assessed were within the pharmacopoeial specifications except for metrogyl product which did not disintegrate within the specified time. Weight variation test showed that all products meet pharmacopoeial specification. Assay results showed that all brands and generic products of metronidazole tablets are within pharmacopoeial limits. The statistical results of the assay of tablets showed that no significant difference between all products ($P>0.05$).

Except metrogyl, all metronidazole tablets included in this study released 85% of labeled amount of drug in the specified time. All products of metronidazole benzoate oral suspensions showed assay results within the pharmacopoeial limit. Statistical results of the assay of metronidazole benzoate oral suspensions showed that there is no significant difference between all products ($P > 0.05$).

Amrizole has relatively moderate viscosity (728.0 ± 0.12 cP), which may cause good pourability of the suspension with a sedimentation value of 1 (acceptable and stable suspension). On the other hand Camezol has low viscosity (9.2 ± 0.40 cP) and sedimentation value (0.10), which may cause faster sedimentation of the particles of the suspension.

All of the assessed formulations of metronidazole possess good quality as demonstrated by passing all the pharmacopoeial requirements except metrogyl, which failed both disintegration and dissolution studies.

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