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Research Article

Comparative *In Vitro* Quality Evaluation of Different Brands of Mebendazole Tablets, Marketed in Mekelle Town, Tigray, Ethiopia

Abraham Gebrezgabiher, Zewdu Yilma*, Ebisa Tadese

Department of Pharmacy, College of Health Sciences, Mekelle University, P.O.Box 1871, Mekelle, Ethiopia.
**Correspondence:* ziedo21@gmail.com/zewdu.yilma@mu.edu.et (Tel.: +251910059272)

Abstract

There are growing concerns that various mebendazole formulations may have different bioavailability and that development of resistance will accelerate if suboptimal doses are used. Despite the considerable use in Ethiopia, there are no reports on the quality assessment of the various brands of mebendazole tablets marketed in Ethiopia. The objective of the present study is to assess physical properties and the quality control parameters of the marketed brands of Mebendazole tablets found in pharmacy outlets in Mekelle, Tigray, Ethiopia. Six different brands of mebendazole tablets were identified, purchased and evaluated for uniformity of weight, friability, hardness, disintegration and assay of active pharmaceutical ingredient and dissolution profile according to established methods, and analyzed using MS excel and Origin pro 8. Results obtained indicated that all brands comply with official requirements for uniformity of weight, hardness and assay. The identification test, which is done using FTIR, indicated that all the samples were mebendazole. Brands showed difference in disintegration times which ranges from 20 seconds to 180 seconds except brand MZ-6 which stays up to 3 hr.Except MZ-6 which releases only 38% with in 75 minute, the other brands released within the range of 96-99%. From this study, it can be concluded that, except brand MZ-6, all brands are comparable and acceptable in their quality. Since MZ-6 showed long disintegration time and poor dissolution profile, its manufacturing process needs to be reviewed.

Keywords: Comparative study, quality assessment, mebendazole tablet, Mekelle.

Introduction

The presence of substandard pharmaceutical products in the drug distribution chain may produce a danger to the public health. Drug quality reports by the United States Pharmacopoeia Drug Quality and Information Program in different countries e.g. Benin, Ghana, Nigeria, Bangladesh, Cambodia and China revealed that a large number of drugs failed quality testing. Some of these drugs were found to contain active ingredients outside the appropriate limits and most of them below the limits. Such drug products have therapeutic as well as social and economic implications [1].

In developing countries, counterfeit and substandard medicines are endemic [2].Marketing of poor quality drugs is high in developing countries, especially of Africa and Asia because of weak drug regulatory systems. Thus, in countries where drug regulatory control is weak, the quality of marketed drug products cannot be guaranteed. Quality assessment studies on some of the marketed drug products could give an insight into the quality of the pharmaceutical products marketed within the distribution chain and consumed. Such studies could provide basis for corrective measures taken by drug regulatory authorities [3].

Mebendazole is one of the most widely used drugs for the control of helminthes. The availability of numerous brands of mebendazole in our drug market today places clinicians and pharmacists in a difficult situation of choice of a suitable brand or the possibility of alternative use. Besides, there are growing concerns that various mebendazole formulations may have different bioavailability and that development of resistance will accelerate if suboptimal doses are used [4]. Despite the considerable use in Ethiopia, there are no studies conducted on comparative in vitro quality evaluation on different brands of mebendazole tablet in Ethiopia in general and in Mekelle in particular. Therefore, the objective of this study is to assess the physical properties and the quality control parameters of the different brands of mebendazole 100mg tablets marketed in Mekelle.

Materials and Methods

Materials

Mebendazole reference standard and 1% sodium lauryl sulfate were obtained as a gift from Addis Pharmaceutical Factory (APF).Six brands of mebendazole tablets were identified and purchased from pharmacies present in the city of Mekelle.All other chemicals and reagents like chloroform, 0.1N HCl, anhydrous formic acid, and 0.5M methanolic hydrochloric acid,were used as received.

Visual inspection and Identification test

The general appearance of all tablets is essential for consumer acceptance. The six brands of tablets bought were evaluated for size, shape and color. The diameter and thickness of the tablets were measured using micrometer screw gauge.

Identification test was done using FTIR as follows:A quantity of the powdered tablet equivalent to 50 mg of mebendazole was shaked with 10ml of a mixture of 10 volume of anhydrous formic acid and 90 volume of chloroform for 30 minutes. Then it was filtered and evaporated to dryness and the residue was dried at a pressure not exceeding 0.7kpa. The infrared absorption spectrum obtained from mebendazole working standard or the reference spectrum of mebendazole was compared with the infrared absorption spectrum obtained from different brands of mebendazole tablets [5].

Hardness

Ten tablets were individually placed carefully in a hardness tester and the degree of force required to break the tablets were recorded. The values were expressed in Newton (N) [5].

Friability test

The friability of tablets was determined by using ERWEKA TA Friabilator. 20 tablets were weighed and placed in the Friabilator and rotated at 25 rpm for 4 min. Then the tablets were taken out, dusted and reweighed. The percentage friability of the tablets were calculated by the formula, Percentage Friability = [(Initial Weight – Final Weight)/ Initial Weight] × 100. Three trials per brand were performed.

Weight variation

Twenty tablets of each brand were selected at random and weighed individually. The weights of individual tablets were noted. Average weights were calculated and the individual weights werecompared with the average weight [5].

Assay

In this study, depending on cost and availability of the instruments, the methods described in BP 2007 were chosen [6].

Standard preparation

50mg of mebendazole working standard was weighed and transferred to a 100 ml volumetric flask and 50ml of 0.5M methanolic hydrochloric acid was added and shaked for 30 min and diluted to 100ml with the same solvent. Then it was filtered and 10ml of the filtrate was diluted to 100ml with 0.5M methanolic hydrochloric acid and mixed. This solution was used as a standard solution.

Sample preparation

Twenty tablets from each brand product were weighed and powdered. Quantities of the powder equivalent to 50 mg of drug were weighed accurately then transferred to a 100ml volumetric flask. 50ml of 0.5M methanolic hydrochloric acid was added and was shaken for 30 min and diluted to 100ml with 0.5M methanolic hydrochloric acid. Then it was filtered and 10ml of the filtrate was diluted to 100ml with 0.5M methanolic hydrochloric acid and mixed. 5ml of filtrate was further diluted to 50ml with the same solvent and mixed.

Then the absorbance of the standard and sample solutions was measured at the maximum at about 234nm using 0.5M methanolic hydrochloric acid in the reference cell. The content of C16H13N3O3 was calculated from the absorbance reading and the declared content of C16H13N3O3 in mebendazole working standard.

Content (mg/tab) = Abs sample/Abs STD x 50/100 x10/100 x5/50 x100/Wt taken x 100/10 x50/50 x purity of std/100 x average weight

Disintegration time

Disintegration test was carried out by using ERWEKA ZT 3 Disintegration test apparatus. One tablet was placed in each tube, and the basket rack was positioned in a 1-litre beaker of distilled water, at 37°C ±2°C. A standard motor-driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 32 cycles per minutes. The time taken for the tablet to disintegrate completely was noted [5].

Dissolution studies

The dissolution rates of mebendazole tablets were determined according to USP XXVII specifications. The dissolution medium consisted of 900 ml 0.1N hydrochloric acid containing 1% sodium lauryl sulfate in a thermostatically controlled water bath at 37±0.5°C. This was stirred at 75 rpm using dissolution apparatus II.

The amount of mebendazole released from the respective tablet products put in dissolution media were determined by sample withdrawal at different times. Samples (5 ml) were withdrawn after 5, 10, 15, 20, 30, 45, 60 and 75 min and an equivalent amount of the same media were immediately introduced. The samples were filtered and suitably diluted with the same medium for the assay of drug content [5].

Data analysis

The collected data were entered and cleaned in Microsoft excel 2007.Then the data were analyzed using Microsoft excel 2007 and origin pro 8 with confidence level of 95%.

Results and Discussion

The tablets were evaluated for various physical parameters such as color, diameter, thickness, hardness, friability, weight variation, identification, dissolution, disintegration time and drug content. The results are presented in Table 1 and in Figure 1.

From the identification test, the result of the infrared spectrometry indicated that all the samples were mebendazole. The effect of transporting the tablets from the factory to the point of sale or consumption is evaluated through the friability test. No sample is expected to lose more than 1% of its weight after the test. This was true for all the brands (Table 1). The study conducted in Cameroon showed that friability test was within the limit for all the brands except for one brand (MBZ5) which lose 1.74% of its weight after the test [7]. Loss of weight of more than 1% is an evidence of poor production which results in tablets not adapted for rough handling and transportation through potholed roads.

There were significant differences in the disintegration time among the various brands of mebendazole tablets ($p < 0.05$) especially between MZ-2 and MZ-3; and between all the brands with MZ-6. The difference may be due to difference in manufacturing process such as compression force, dwell time as well as tablet composition such as disintegrants. Brands MZ-4, MZ-2 and MZ-4 recorded fastest disintegration times of 20 sec., 45sec. and 60 sec. respectively. The disintegration time values recorded for the other three brands were found to be in the range of 3 min to 3 h (Table 1 and Table 2).

Table 1. The color, diameters, thickness, weight and hardness of mebendazole tablets*

Code	Color	Diameter (mm)	Thickness (mm)	Weight variation(mg)	Hardness (N)
MZ-1	Pink	9.50±0.04	3.08±0.13	265.37±8.16	66.8±1.86
MZ-2	Orange	7.90±0.01	2.97±0.11	176.49±4.60	39.9±0.57
MZ-3	Orange	9.43±0.01	3.57±0.06	283.12±2.84	55.5±0.67
MZ-4	Pink	9.41±0.00	3.01±0.12	300.96±9.09	70.4±1.29
MZ-5	Beige	9.94±0.02	3.26±0.06	310.54±1.76	75.1±0.65
MZ-6	Beige	9.46±0.08	3.19±0.06	294.94±5.51	49.5±0.53

**Values are in the form of Mean ±SD*

Table 2. The friability, disintegration time, assay, DE (%) and drug release characteristics of mebendazole tablets

Code	Friability %	Disintegration time (sec)	Assay (%)	DE (%)	% Release
MZ-1	0.24	60	96.68	71.80±2.2	97.00
MZ-2	0.16	45	95.06	76.20± 2.8	98.33
MZ-3	0.37	232	95.24	64.24±3.6	96.00
MZ-4	0.07	20	98.86	78.32±3.2	98.60
MZ-5	0.11	245	98.30	67.12± 4.2	98.17
MZ-6	0.21	9000	96.71	13.33± 1.8	38.00

**Values are in the form of Mean ±SD*

The Mebendazole tablets tested were chewable tablets. Chewable tablets are intended to disintegrate smoothly in the mouth at a moderate chewing, and ingested with little or no water. Characteristically chewable tablets should be easily crushed by chewing and have a smooth texture upon disintegration [8]. In practice, patients may swallow chewable tablets without chewing (even though the label states "must be chewed"). This is not a simple concern in the study area and other parts of the country where

dispensers do not provide appropriate patient counseling due to high patient load, lack of knowledge and lack of updated drug information [9-11]. Tablet disintegration is a prerequisite for dissolution and drug absorption.So, disintegration time of 3 h for MZ-6 is unacceptably high. Poor disintegration time values could mean that the manufacturing process such as compression force, dwell time as well as tablet composition (like disintegrant) needs to be reviewed.

The hardness was found in the range of 32.9 to 95.6 N for all the brands indicating good mechanical strength. It can easily be seen from the tables that the disintegration time seems to be not related to hardness. The more a tablet is hard; its disintegration time is not long. MZ-5 had hardness of 75.1N with disintegration time of 245sec. whereas MZ-6 had hardness of49.5N with disintegration time of 2.5h.

UV spectrophotometric analysis of the brands yielded that drug content results were within acceptable pharmacopoeial range. According to the standard of the Indian pharmacopoeia, mebendazole tablet should contain 95 to 105% of the claimed label of the active ingredient. By this standard, all brands were found to contain active ingredient within the accepted limit.

The results of dissolution studies are graphically represented (Figure 1). All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results.

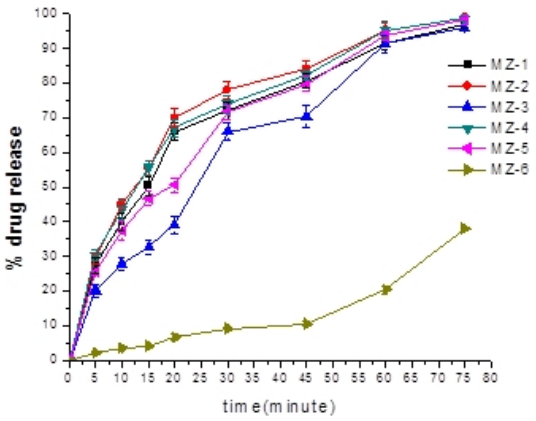

Figure1. Dissolution profiles of all brands of mebendazole tablets

All the brands released more than 95% active ingredient of the drug within 75 min except MZ-6. The released amount was in the range of 96-98% for all the brands indicating good releasing profile, except MZ-6 which is 38%.The fact that the mebendazole brand MZ-6 did not meet dissolution rate requirements raises a great concern about the efficacy of the brand marketed in mekelle. Albonico and his coworkers indicated that albendazole preparations that fail dissolution testing achieved lower egg reduction rates than preparations that meet dissolution requirements [12]. Dissolution is a prerequisite for the availability of the active drug for absorption by parasite tissue or patient.

There were significant differences in the dissolution profile among the various brands of mebendazole ($P<0.05$). There was a significant difference between MZ-2 and MZ-3; and between all the brands with MZ-6. The difference may be due to difference in manufacturing process such as compression force, dwell time as well as tablet composition or lack of disintegrant excipients.

Again dissolution efficiency (DE) was also employed to compare the drug release from various brands. Dissolution efficiency is the area under the dissolution curve within a time range (t1 - t2) expressed as a percentage of the dissolution curve at maximum dissolution, over the same time frame. This was calculated from the equation:

$$DE = \frac{\int_{t1}^{t2} y_{dt}}{y_{100}\, x(t2-t1)}$$

Where y is the percentage of drug dissolved at time t [13].

ANOVA revealed significant differences in DE values for all tablet formulations ($P < 0.05$) except for MZ-2 versus MZ-4 (DE, 76.2 ± 2.8 versus 78.32 ± 3.2; $P = 0.226$). Products MZ-4 and MZ-2 showed higher dissolution efficiency (78.32 ± 3.2 and 76.2 ± 2.8, respectively); while other exhibited a dissolution efficiency within the range of 64- 72 except MZ-6 which is 13.33 ± 1.8. On the basis of dissolution efficiencies of the tested products, significant differences were found in their dissolution performances.The difference may be due to difference in the formulation and manufacturing process.

Conclusion

All brands comply with official requirements for the different physical properties and the quality control parameters except MZ-6 which shows poor dissolution profile and long disintegration time. Among the brands, brand MZ-4 showed better characteristics of chewable tablets. From this study, it can be concluded that, except brand MZ-6, all brands are comparable in their quality. Since MZ-6 shows poor dissolution profile and long disintegration time values, it means that the manufacturing process such as compression force, dwell time as well as tablet composition (like disintegrant) needs to be reviewed. To assure the safety of the public and to prevent drug resistance, drug regulatory authority of Ethiopia (Food, Medicine and Health Care Administration and Control authority of Ethiopia) should work on quality assessment of the different brands of drugs marketed in the country and take corrective measures.

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Conflict of interest

The authors declared no competing interests.

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