Comparative *In Vitro* Quality Evaluation of Different Brands of Ibuprofen Tablets Marketed in Mekelle, Ethiopia

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Research note

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Abstract

Objective Quality of pharmaceutical products is required to guarantee their safety and efficacy. The aim of this study was to evaluate the physicochemical quality attributes of different brands of ibuprofen tablets marketed in Mekelle, Ethiopia. The methods stated in the British Pharmacopeia were adopted for weight uniformity, hardness, friability, disintegration test and assay of drug content. Dissolution test was also carried out as stated in the United States Pharmacopeia. To compare dissolution profile, statistical analysis of drug release at different time points were employed.

Results All the brands were found with acceptable pharmacopeial specifications for weight uniformity, friability, hardness, assay of drug content and dissolution test. Six brands fulfilled the pharmacopeial requirements of disintegration test while one brand failed to disintegrate as per the BP specification. However, there were statistically significant difference in weight, hardness, disintegration, dissolution and amount of drug content among the tested samples. Thus, from this study we can conclude that all the products fulfilled the required quality evaluation parameters as stipulated in pharmacopeias except one brand which failed the disintegration test. However, the *in vitro* dissolution profile indicated that there may be a potential bio-in equivalence among the pharmaceutical products.

1. Introduction

Generic medicine is a pharmaceutical product that can be interchangeable with the innovator medicine. Generic medicine is the same as its corresponding innovator medicine in terms of quality, safety, efficacy, strength, dosage form, route of administration and intended use [1–3]. However, there are misperceptions that generic medicines are less effective than branded drugs and/or generic drugs are poor quality as compared to brand medicines by health care providers and patients [4].

There are many pharmaceutical companies and distribution channels of drugs worldwide. Unfortunately, circulation of poor quality drug products in the international market increase significantly as a result of ineffective regulation of manufacturing and trading of pharmaceutical products [5]. Therefore, the manufacturing, distribution, storage and use of drugs need to be regulated authorized regulatory institutions [6].

Poor quality medicines are public health problems that affect both developing and developed countries [7, 8]. According to the World Health Organization, in low and middle-income countries 10% of the medical products are either substandard or falsified [9]. Since, Ethiopia is one of the low-income countries, falsified or substandard medicines could be available in the market. These could be due to lack of adequate resources, weak regulatory enforcement, weak port control, lack of informal market control, poor cooperation between executive bodies and resource constraint [6, 10]. Poor quality drug products could cause treatment failure, increased mortality and morbidity, drug resistance and economic loss [11].

Ibuprofen is one of the commonly used generic none steroidal anti-inflammatory drug in the world. It has analgesic, anti-inflammatory and anti-pyretic activities [12]. The main purpose of this study was therefore

to evaluate the quality of different brands of ibuprofen products available in drug retail outlets in Mekelle, Ethiopia.

2. Materials And Methods

2.1 Materials

Reference standard of ibuprofen was obtained from Addis Pharmaceutical Factory and seven brands of 400 mg film coated ibuprofen tablets were randomly purchased from different pharmacies and drug stores in Mekelle.

2.1.1 Instruments and equipment

Liquid Chromatography (Agilent 1260 series, Germany), PG double beam ultraviolet/visible (UV/VIS) spectrophotometer (T80 Instruments, England), Adwa pH meter (AD8000 Instuments, Romania), electronic balance (Mettler Toledo, Switzerland), Hardness, friability, disintegration and dissolution testers all from Pharm Test, Germany were used in the study.

2.1.2 Chemicals and reagents

Methanol (Loba Chemie), potassium dihydrogen orthophosphate (Loba Chemie, India), orthophosphoric acid (Sigma-Aldrich, Germany) and distilled water (Jourilabs, Ethiopia) were used for the analysis.

2.2 Methods

Weight uniformity, hardness, friability, disintegration, dissolution and assay of drug content were performed based on specifications stipulated in the British Pharmacopeia (BP) and the United State Pharmacopeia (USP).

2.2.1 Weight uniformity

From each brand, twenty tablets were randomly selected, weighed individually and then average weight was determined. Then percentage deviation of individual weight from average weight was calculated [13].

2.2.2 Hardness

The crushing strength of the tablets was determined by selecting randomly ten tablets from each brand and measuring their hardness by using a hardness tester apparatus [13].

2.2.3 Friability

Twenty tablets from each brand were weighed using an analytical balance. These tablets were placed in the drum of the friability tester and subjected to rotation at 25 revolutions per minute (rpm) for 4 minutes.

The tablets were removed from the apparatus and weighed again. Percent friability was calculated for each drug product [13].

2.2.4 Disintegration

Disintegration of the products was determined in 900 mL of distilled water as stipulated in the BP. The temperature of the medium was maintained at 37 ± 2 ^{o}C. One tablet was placed in each of the six tubes, then the basket rack assembly started to move up and down. The tablets were considered disintegrated when all of the particles pass through the mesh screen. If any residue remains, it must be fragments of insoluble coating. The time in minutes required to disintegrate for each tablet was recorded and average disintegration time for each product was calculated [13].

2.2.5 Dissolution

A calibration curve (Fig. 1) was constructed using ibuprofen reference standard to evaluate the drug release of the products. Ten mg of standard ibuprofen was dissolved in a 100 mL volumetric flask using a phosphate buffer pH 7.2. After gentle shaking, the volume was made up to 100 mL using the same solvent and that solution was used as the stock solution. From this solution, concentrations corresponding to 1, 2, 4, 6, 8 and 10 µg/mL were prepared. After filtration, the absorbance of the filtrate was measured at a wavelength of 221 nm using UV/VIS spectrophotometer. The buffer was used as a blank. Then, a calibration curve of absorbance against its corresponding concentration was constructed [14].

Dissolution test of ibuprofen tablets was employed by using USP apparatus II (paddle method) [15]. For each brand, in each of the six vessels, phosphate buffer (900 mL, pH 7.2) at 37 ± 0.5 ^{o}C was used as a dissolution medium. The rotation of the paddle was set at 50 rpm. Filtered sample solutions (10 mL) were withdrawn at 10, 20, 30, 45, 60, 75 and 90 minutes. After appropriate dilution the absorbance of was measured by UV/VIS spectrophotometer at 221 nm. The dissolution medium was used as a blank. The concentration of drug released at each time point was determined using the calibration curve. Dissolution profile among the products of ibuprofen tablets were carried out by statistical analysis of drug release at different time points [16].

2.2.6 Assay of active ingredient

A mobile phase was prepared with orthophosphoric acid, distilled water and methanol (3:247:750, v/v/v). Standard ibuprofen solution was prepared with a concentration of 2 mg/mL. The solution was filtered by 0.45 µm membrane filter then injected into the HPLC system. The analysis was performed using shodex C_{18} column (25 cm × 4.6 mm, 5 µm) at a temperature of 30 ^{o}C, flow rate of 0.75 mL/min and injection volume of 20 µL. Detection was performed at 264 nm [13].

Sample solution was prepared using twenty tablets from each brand then weighed and powdered by mortar and pestle. A powdered sample equivalent to 0.2 g of ibuprofen was dissolved in 30 mL of mobile phase and then diluted to volume (100 mL). From this solution, 25 mL was taken and centrifuged at

2500 rpm for 5 minutes. Filtered supernatant sample solution was analyzed by using HPLC system as described above for the reference standard.

3. Results And Discussion

3.1 Weight uniformity

Weight variation of the tablets indicates variation in amount of active ingredient (API) and/or excipient (s). Variation in amount of API may lead to toxicity, ineffectiveness or unpredictable action of the drug products. Variation in amount of excipient/s may also affect other physicochemical characteristics of the product and ultimately it may alter the bioavailability and therapeutic activity of the drug [13, 17]. Therefore, weight variation among unit dosage forms should be within narrow range. The results (Table 1) indicated that weight uniformity of the brands was within the acceptable limit as stated in the BP specifications [13]. There exists statistically significant difference among the brands mean weight ($p < 0.0001$). This could be due to the fact that manufacturers may use different amounts of additives and/or API in varying proportion for the drug products.

Table 1
Results of weight, hardness, friability and disintegration time and drug content of seven brands of ibuprofen tablets (13, 15, 19).

Brand code	Mean weight (mg) ± RSD[a]	№ of tablets with weight variation > 5%	№ of tablets with weight variation > 10%	Hardness (N) (mean ± RSD)	Percent of friability	Mean disintegration time (min)	Drug content (%) ± RSD
IBU-A	608 ± 1.96	1	0	102.98 ± 19.14	0.03	3.12	98.00 ± 0.06
IBU-B	703 ± 0.85	0	0	162.44 ± 6.29	0.04	5.08	99.30 ± 0.01
IBU-C	536 ± 1.00	0	0	128.22 ± 4.12	0.01	21.17	104.55 ± 0.04
IBU-D	522 ± 1.19	0	0	117.18 ± 19.57	0.04	4.68	96.06 ± 0.07
IBU-E	542 ± 1.07	0	0	105.48 ± 6.20	0.03	39.10	100.39 ± 0.02
IBU-F	576 ± 0.68	0	0	85.42 ± 9.84	0.01	6.82	95.25 ± 0.03
IBU-G	576 ± 1.23	0	0	132.42 ± 3.37	0.02	8.77	100.72 ± 0.00
specification		≤ 2 tablets	None	¬ 40 N	≤ 1%	≤ 30 min	95–105%

3.2 Hardness

Tablet hardness is the measure of the force required to break tablets in diametric compression [18]. It should not be so low that the tablets are soft and may not be able to withstand conditions of storage, handling and transportation without breaking. Conversely, tablets should not be too hard because they may not disintegrate in the required period of time and it may affect the dissolution and bioavailability of the drug product. Hardness is one of the quality evaluation parameter of tablet dosage forms– and should be above 40 Newton [19]. All of the examined products (Table 1) complied with the specifications. There was a significant difference in their mean hardness ($p < 0.0001$) among the different brands of ibuprofen tablets. Manufacturers may use different method of production including a difference in the method of granulation, compression force and excipients resulting in variation of tablet hardness [20].

3.3 Friability

Friability (F) was conducted to evaluate the ability of tablets to withstand abrasion to packaging, handling and transporting [21]. If tablets are less friable, they will maintain good appearance without becoming dusty during storage, transporting or dispensing. On the other hand, if tablets are highly friable,

patient acceptability of the medicine may decrease and the patient may get under dose because of abrasion of the tablets then ultimately treatment failure may occur. According to the BP, if the %F of tablet is not greater than 1%, the test complies [13]. As shown in Table 1, the %F was found in the range of 0.01–0.04%.

3.4 Disintegration

According to the BP specification, film-coated tablets should be disintegrated within 30 minutes [13]. All of the samples disintegrated within the acceptable tolerance limit of film-coated tablets except IBU-E which disintegrated after 39.1 minutes (Table 1). A one-way analysis of variance (ANOVA), showed that there was a significant difference ($p < 0.0001$) in mean disintegration time among the different products of ibuprofen tablets.

3.5 Dissolution

Dissolution of tablet dosage form is related to the absorption and bioavailability of drugs [18]. Results indicate that all of the studied ibuprofen tablets released more than 80% within 60 minutes (Fig. 2) and hence fulfilled the official dissolution requirements as stipulated in the compendia [15]. Drug product IBU-C had the highest percentage of drug release (98.45%) while IBU-E was the least with percentage drug release of 87.67% at 60 minutes.

The availability of various brands of medicines (e.g. ibuprofen) put health care professionals and patients into confusion about which brand to choose and the possibility of interchangeability among the brands [22]. In order to ensure interchangeably, bioequivalence study is required. To verify this, a similarity in rate and extent to which the drug in the dosage form become available for absorption need to be investigated. *In vitro* bioequivalence study among different products can be carried out using different methods. In cases when greater than 85% of the drug is dissolved within 15 minutes, dissolution profiles are usually considered as similar without further evaluation [23]. However, all of the products dissolution rates did not meet 85% dissolution within 15 minutes and were subjected for further statistical evaluation to demonstrate bioequivalence. A one-way ANOVA indicated that the brands had statistically significant difference ($p < 0.0001$) in mean drug release at the tested time points (10, 30, 60 and 90 minutes). This could be due difference among manufacturers in the method of production such as use of different excipients (amount and type) and varying amount of API [22]. The results have shown that continuous quality evaluation of the multisource drug products is required for rational decision making regarding their quality and interchangeability. The difference in dissolution rate among the different brands might influence the drug products effectiveness and side effect.

3.6 Assay of active ingredient

All of the brands (Table 1) were within the acceptable limit according to the BP (95 and 105%) [13]. A one-way ANOVA indicated that there is a significant difference in mean drug content ($P < 0.0001$) among the samples investigated in this study.

Conclusion

All of the evaluated products of ibuprofen tablets marketed in Mekelle were within the acceptable compendial limits based on the *in vitro* results of the study except product IBU-E which failed in the disintegration test. However, among the brands there were statistically significant differences in their weight uniformity, hardness, disintegration, assay of their active ingredient. The comparative dissolution profile of the drugs has shown potential significance difference among the products which raises a doubt about the interchangeability. It is advisable that the Ethiopian Food and drug Administration and Regional Health Bureau should control the quality of drugs at various levels in the market on regular basis.

Limitations

For this study, small number of brands (those only available during the study period) was evaluated to assess the quality. Increasing the number of brands could have given comprehensive picture about the quality of ibuprofen tablets in Ethiopia

HPLC: High performance liquid chromatography; BP: British pharmacopoeia; USP: United Sates pharmacopoeia; rpm: revolution per minute; UV/Vis: Ultraviolet –visible spectroscopy; API: Active pharmaceutical ingredient; ANOVA: Analysis of variance.

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Declarations

Acknowledgments

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Declaration

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing Interests

The authors declare that they have no any competing interests.

Availability of data and materials

The datasets supporting the conclusions of the study are included in the article. Any additional data will be available on request.

Competing Interests

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Author Contributions

BG and GK conceived the study. BG, GK, TE, and HG performed the investigation and interpretation of the analytical data. BG wrote the first draft. BG, GK, TE and HG contributed to the substantive revision of the final draft. All authors read and approved the final manuscript.

References

1. World Health Organization (WHO). Glossary of Globalization, Trade and Health Terms. 2012; Available from: http://www.who.int/ trade/glossary/story034/en/index.html (accessed on May 29, 2018)
2. Davit BM, Nwakama PE, Buehler GJ, Et a l. Comparing Generic and Innovator Drugs : A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration. Ann Pharmacother S. 2009;43:1583–97.
3. Cameron A, Laing R. Cost Savings of Switching Private Sector Consumption from Originator Brand Medicines to Generic Equivalents. World Health Organization Report; Background Paper. 2010;35:210–5.
4. Patel VP, Kishnani TK. A Survey Based Exploratory Study Evaluating Chemist's Knowledge, Attitude, Concerns and Experience Regarding Generic Medicines in Urban Central Gujarat Region. Int J Sci Res Sci Eng Technol. 2017;3(3):470–5.
5. Binega G, Wondimsigegn D, Tsega B. Analysis and Comparison of Paracetamol Tablets Dispenced in Legal Dispenceries and Non Pharmaceutical Shopes in Gonder Town, North West Ethiopia. Int J Pharm Ind Res. 2013;3(2):144–51.

6. Kahsay G, Debella A, Asres K. Comparative In Vitro Quality Evaluation of Ciprofloxacin Tablets from Drug Retail Outlets in Addis Ababa , Ethiopia. Ethiop Pharm J. 2007;25:1–8.
7. Dégardin K, Roggo Y, Margot P. Understanding and Fighting the Medicine Counterfeit Market. J Pharm Biomed Anal. 2014;87:167–75.
8. Chika A, Bello SO, Jimoh AO, Umar MT. The Menace of Fake Drugs: Consequences, Causes and Possible Solutions. Res J Med Sci. 2011;5(5):257–61.
9. World Health Organization (WHO): Fake Drugs Are A Major Global Problem , WHO Reports. 2017; Available from: https://www.npr.org/sections/goatsandsoda/2017/11/29/567229552/bad-drugs-are-a-major-globalproblem-who-reports (accessed on May 15, 2018)
10. Suleman S, Woliyi A, Woldemichael K, Tushune K, Duchateau L, Degroote A, et al. Pharmaceutical Regulatory Framework in Ethiopia : A Critical Evaluation of Its Legal Basis and Implementation. Ethiop J Heal Sci. 2016;26(3):259–76.
11. Newton PN, Green MD, Fernández FM. Impact of Poor-Quality Medicines in the “Developing” World. Trends Pharmacol Sci. 2010;31:99–101.
12. Rainsford KD. Ibuprofen: Pharmacology, Efficacy and Safety. Inflammopharmacology. 2009;17(6):275–342.
13. British Pharmacopoeia. The Her Majesty’s Stationery Office: London; 2013; Vol I-III.
14. Giri TK, Manjusha. Comparative In Vitro Evaluation of Conventional Ibuprofen Marketed Formulation. J PharmaSciTech. 2013;2(2):75–80.
15. US Pharmacopoeia/ National Formulary, USP 41/NF 36. United States Pharmacopoeia Convention Inc., Rockville, MD, USA; 2017.
16. Ashraful-Islam SM, Dewan I, Shahriar M, Bin Sayeed MS. Validation and Application of a Simple HPLC Method for the Comparative In Vitro Dissolution Study of Some Multisource Ciprofloxacin Tablets. IJPI’s J Anal Chem. 2012;2(8):1–12.
17. Ogah CO, Kadejo FF. Analysis of Brands of Glibenclamide Tablets in Lagos Market. J Innov Res Eng Sci. 2013;4(2):466–71.
18. Dewan SM, Alam A, Ahamed SK. A Comparative Quality Control Study on Conventional Ibuprofen Tablets Available in Bangladeshi Pharma Market. Int Res J Pharm. 2013;4(1):96–8.
19. Allen LV, Popovich NG, Ansel HC. Pharmaceutical Dosage Forms and Drugs Delivery System. 9th ed. Troy DB, editor. Walters Kluwer/ Lipincott Williams & Wilkins; 2009. 233 p.
20. Khreit OI, Alkailani HA, Alqathafı WS. A Comparative Study of Physical and Chemical Parameters of Selected Paracetamol Tablets Available in the Pharma Market of Libya. Der Pharma Chem. 2017;9(2):1–6.
21. Sahle SB, Ayane AT, Wabe NT. Comparative Quality Evaluation of Paracetamol Tablet Marketed in Somali Region of Ethiopia. Int J Pharm Sci Res. 2012;3(2):545–50.
22. Hailu GS, Gutema GB, Hishe HZ, Ali S, Asfaw AA. Comparative In vitro Bioequivalence Evaluation of Different Brands of Amoxicillin Capsules Marketed in Tigray , Ethiopia. Int J Pharm Sci Nanotechnol.

2013;6(1):1966–71.

23. Hailu GS, Gutema GB, Asefaw AA, Hussen DA, Hadera MG. Comparative Assessment of the Physicochemical and In Vitro Bioavailability Equivalence of Co-trimoxazole Tablets Marketed in Tigray, Ethiopia. Int J Pharm Sci Res. 2011;2(12):3210–8.

Figures

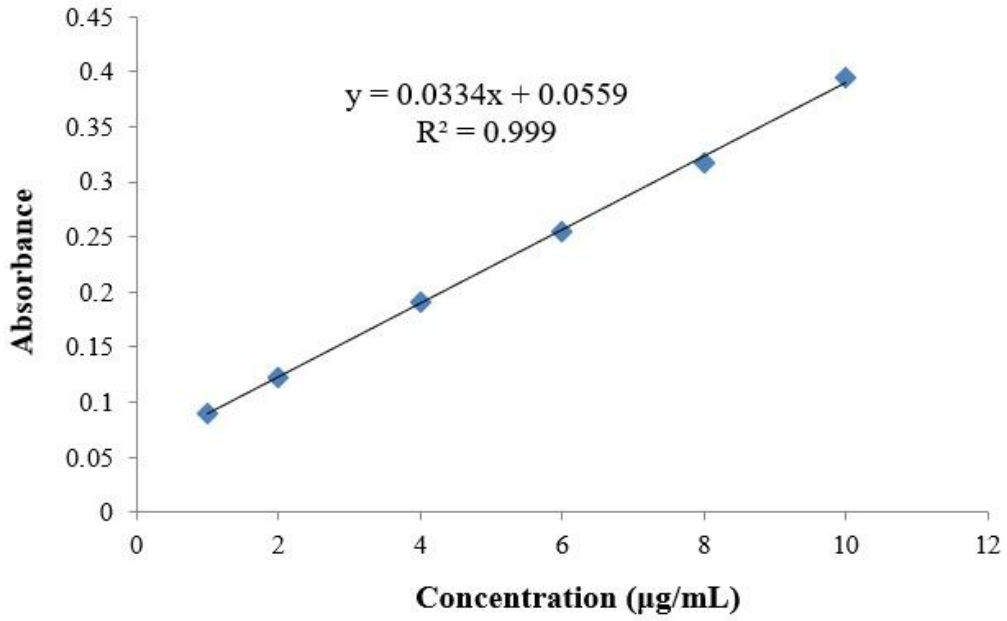

Figure 1

Calibration curve for drug release determination using ibuprofen standard.

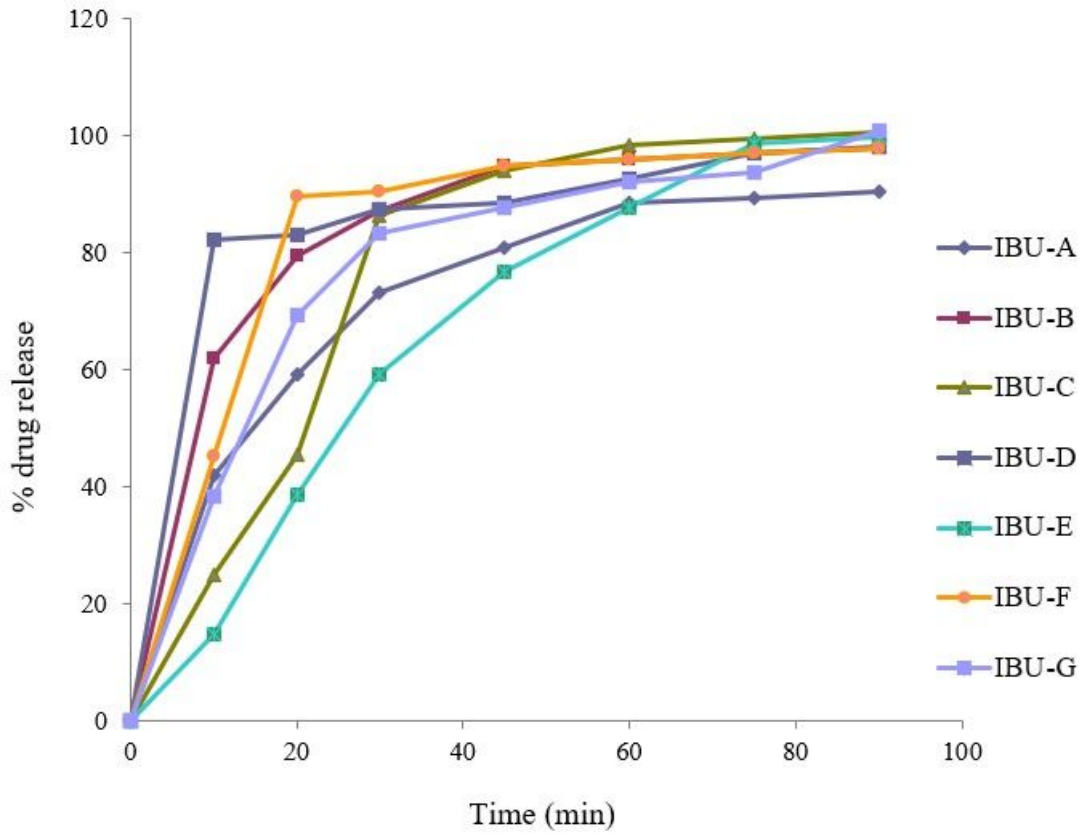

Figure 2

Dissolution profile of seven brands of ibuprofen tablets