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SHORT COMMUNICATION article

The impact of tablet shape on quality control parameters for metronidazole tablet marketed in Libya

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Abstract: Worldwide, various metronidazole brands are manufactured and are imported to the Libyan market which are considered pharmaceutically equivalent but may differ in characteristics such as shape, packaging, excipients, etc. This issue has become a valuable topic for researchers due to the lack of information on the effective quality of the tablets about their shapes. The purpose of this study was to assess the pharmaceutical quality of two metronidazole tablet brands with different shapes that are available for purchase in Libya and to figure out how the shape differences impact metronidazole tablet quality. For this purpose, two shapes of metronidazole tablets, round and oblong, were used. The quality control characteristic parameters of a tablet, such as its weight variation, content uniformity, hardness, friability, disintegration, and dissolution were evaluated. The procedures described in the United States Pharmacopoeia (USP) were followed for the tests. All round and oblong tablets passed the weight variation, content uniformity, friability, disintegration time, and dissolution tests that complied with the USP specifications, except for the hardness test, which round and oblong tablets failed to pass. The findings indicated that the shape variations do not affect on the metronidazole tablet quality parameters. The choice of shape of a tablet depends on improving its mechanical qualities, its handling convenience, its packing, and its visual appeal.

Introduction

One of the advantages of administering oral medications is improved patient compliance. Tablets represent the majority of solid dosage forms that are taken orally [1]. Because of their lower manufacturing and packing costs, superior packaging, and increased stability over oral drugs, tablets are the dosage form of choice for manufacturers [2]. Powder compaction studies have gotten substantial funding and effort from the pharmaceutical industry, and because the patient can self-administer the tablet, which is available in a variety of shapes and colours and provides active ingredients constantly, the cost is appropriate [3]. The FDA's requirement of being able to visually identify tablets, combined with the international acceptance of colours, has resulted in the manufacture of tablets with a variety of shapes as a means of identifying the product [4]. Tablets can be disc-shaped or have convex surfaces, but they can also be round, oval, oblong, or cylindrical [5]. Tablet shape could affect patient compliance with treatment regimens. Certain tablet shapes might be simpler to swallow than others. Human studies have shown that compared to round-shaped tablets, the

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swallowing of oval-shaped tablets might be easier and have shorter oesophageal transit times for the same-weight tablet [6]. According to Kadiri and Michrafy [2], there are no issues with the tablet's shape complexity when it comes to pharmaceutical powder compression. The pharmaceutical industry considers tablet shape to be a significant subject since it impacts product development, operating conditions for processes, and marketing concerns [7]. Due to there is a direct correlation between tablet quality and shape, manufacturers should not undervalue the significance of producing an appropriate-shaped tablet with an optimal therapeutic profile while elucidating the rationale behind different oral dosage forms [8]. Ensuring the overall quality of a product is crucial in the pharmaceutical industry to avoid non-compliant products that do not meet Pharmacopoeia specifications. It is necessary to control errors that may occur during the production process [9]. The tests for content uniformity, weight variation, hardness, friability, disintegration, and dissolution are used as quality control measures for pharmaceutical tablets [10].

Metronidazole is a medication that treats diseases brought on by anaerobic bacteria and protozoa. It has antibacterial, anti-amoebic, and antiprotozoal properties [11]. The Libyan market has a wide variety of metronidazole tablet brands that are produced by several international companies [12]. Pharmaceutically equivalent brands vary somewhat in shape, packaging, excipients (colures, flavours, and preservatives), expiration date, and labelling requirements, but they must meet the same compendial or other applicable standards and contain the same amount of active ingredient in the same dosage form [13-15]. This study aims to evaluate and investigate the pharmaceutical quality parameters of tablets of two differently shaped brands of metronidazole drug marketed in Libya, and to determine how the quality of metronidazole tablets is affected by shape variations.

Materials and methods

Two different brands of metronidazole tablets (500 mg) were used in this study with a different shape: one is round (MET-1) while the other is oblong (MET-2). Both metronidazole tablets were purchased from a pharmacy located in Al-Bayda City, Libya. **Table 1** shows the label information for the two brands of metronidazole tablets (500 mg).

Table 1: Label information for two brands of metronidazole tablets

Code	Shape of tablet	Name of company	Country of origin	Expiry date	Batch number
MET-1	Round	A	Egypt	09/2025	CEG102
MET-2	Oblong	B	Egypt	06/2027	8015146A

Analytical method of establishing the standard metronidazole calibration curve: To determine the drug's wavelength of maximum absorbance (λ_{max}) of the metronidazole reference standard (Sigma-Aldrich, USA), a stock standard solution was prepared first by dissolving 50 mg of metronidazole reference standard powder in 100 ml of 0.1 N HCL. 5.0 ml of this solution was transferred to a volumetric flask, and the volume was adjusted to 100 ml with 0.1 N HCL and scanned from 200 nm to 400 nm with a UV-Vis Spectrophotometer (Thermo Fisher Scientific, USA). A range of metronidazole concentrations from 02.5 to 40.0 µg/ml was prepared by making a dilution of the stock standard solution (500 µg/ml), and the solutions were evaluated spectrophotometrically at the drug's λ_{max} = 286 nm using a UV-Vis Spectrophotometer. **Figure 1** shows the calibration curve of the metronidazole reference standard and uses the linear regression equation (y = 0.028x + 0.0301) of the calibration curve to calculate the concentration of metronidazole in sample solutions [13].

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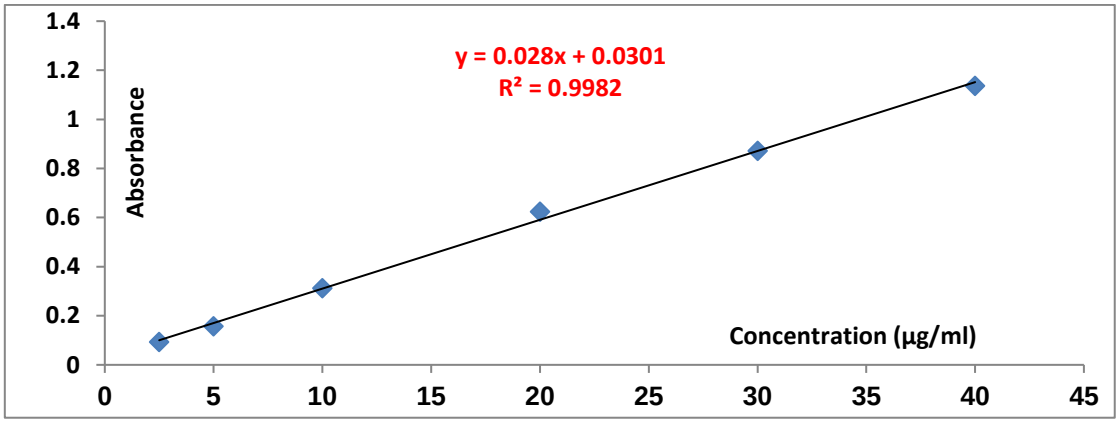

Figure 1: Metronidazole's calibration curve in 0.1 N HCL

Pharmaceutical quality control tests performed in vitro: The average weight for each brand was calculated by weighing twenty tablets individually for each brand using an electronic balance (Sartorius, Mettler Toledo, Germany) [16]. The average hardness was calculated by measuring the hardness (Kg/cm^2) of ten randomly selected tablets from each brand using the TBH 220 D hardness tester (Erweka GmbH, Heusenstamm, Germany) [16]. The friability (%) was calculated by using the formula below: weigh 20 tablets of each brand (W_1) and put in a friability tester (Erweka TAR 220, Erweka GmbH, Heusenstamm, Germany), which was then run for four minutes at 25 rpm. After that, the tablets were re-weighed (W_2) [17].

$$\% \text{ of Friability} = \frac{\text{Initial weight (W1)} - \text{Final weight (W2)}}{\text{Initial weight (W1)}} \text{ X } 100$$

This test was carried out using USP disintegration equipment (Hanson Research, Chatsworth, USA). Six tablets of each brand were used to determine the disintegration time. Each tube contained one tablet, and the basket rack was set inside a 1000 ml vessel containing 900 ml of water that had been maintained at 37.0±0.5 °C. The basket holding the tablets had to be raised and lowered at 32 cycles per minute using a motor-driven apparatus. To prevent the tablets from floating, perforated plastic discs were utilized. The time required for six tablets to break down into small particles and enter the disintegration medium was estimated [18]. The drug content of each tablet was estimated individually using ten tablets selected randomly from each brand and the following procedure: A standard solution (20 µg/ml) of metronidazole reference standard was prepared using 0.1 N HCL as the solvent. A sample stock solution was prepared where one tablet was put in a volumetric (250 ml) flask and 100 ml of 0.1N HCL was added and shaken for 30 min. Complete to volume with 0.1 N HCL, mix, and filter. To prepare a sample solution, 1.0 ml of the filtrate is put into a volumetric (10 ml) flask and diluted to obtain a 0.2 mg/ml solution of metronidazole. Following that, 1.0 ml of this solution is put into a volumetric (10 ml) flask, complete with 0.1 N HCL to volume, and mixed. Using a spectrophotometer to measure the absorbances of the sample and standard solutions at λ_{max} = 286 nm, 0.1 N HCL is used as the blank. The metronidazole quantity (mg) in each tablet is calculated as TC/D - Au/As. Whereas T represents the labelled amount (mg) of metronidazole in the tablet, C represents the concentration (µg/ml) of the metronidazole reference standard in the standard solution, D represents the concentration (µg/ml) of metronidazole in the test solution, based on the labelled amount per tablet and the extent of dilution, Au and As are the absorbances of the sample and standard solutions, respectively [19]. The dissolution test was performed using the Erweka DT600 (Erweka GmbH, Heusenstamm, Germany). Nine hundred millimetres at 37.0±0.5 °C of 0.1 N HCl was used as the dissolution medium. The speed of rotation was 75 rpm. After time intervals of 15, 30, 45, and 60 min, a sample of 5.0 ml was withdrawn and then filtered. The filtrates were then diluted with 0.1 N HCl, and at λ_{max} = 268 nm, the absorbance was measured. Sample concentrations at each of the times mentioned above were calculated by applying the equation of y = 0.028x + 0.0301 which

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was derived from the standard curve of the metronidazole reference standard. The average cumulative release amount and percentage of drug released were determined by using six tablets [5].

Statistical analysis: A Student *t*-test was used to compare the groups. Data are mean±SEM, n = 6-10.

Results and discussion

Weight variation test: Separately, 20 tablets of oblong and round metronidazole were examined for variations in weight. **Figures 2 and 3** show the average weight of round (MET-1) and oblong (MET-2) shaped metronidazole tablets, respectively. The graph includes the minimum and maximum weights of each brand.

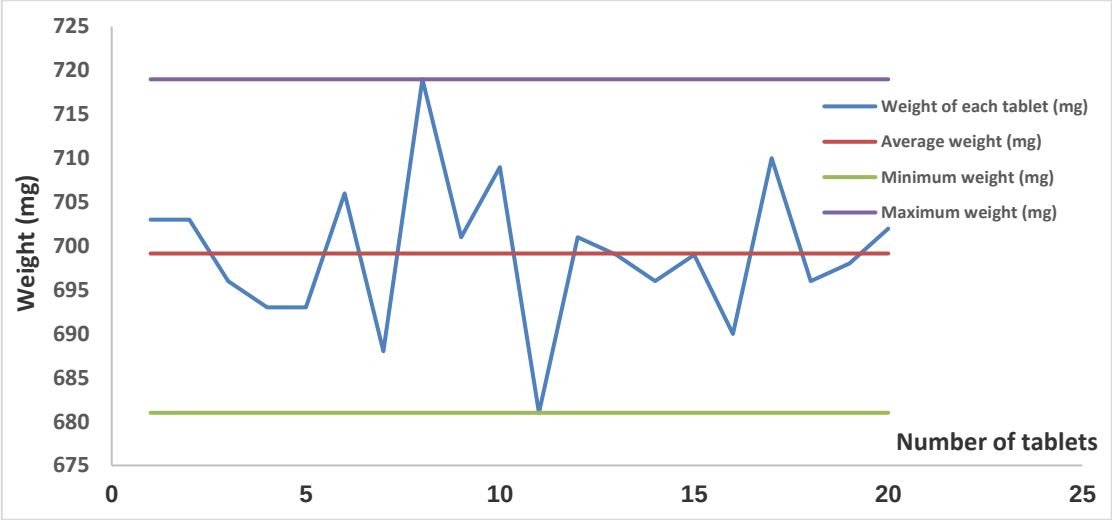

Figure 2: Weight variation test of MET-1 (round-shaped metronidazole tablets)

The findings demonstrated that metronidazole tablets with round and oblong shapes meet USP weight requirements (the percentage weight variations should not exceed ± 05.0% for tablets weighing more than 324 mg) [20]. Although oblong tablets have an average weight greater than that of round-shaped tablets, all round and oblong metronidazole tablets pass the weight variation test with ease. Powder blends are usually compacted in a tablet press, which is a multi-component integrated processing unit. Tablet presses' designs can be influenced by the tooling, such as the die cavity that defines the tablet's shape and size and the punch geometry and size that can be adjusted to provide a suitable weight and shape for the tablet. Weight variability and tablet weight are impacted by die-fill uniformity [21].

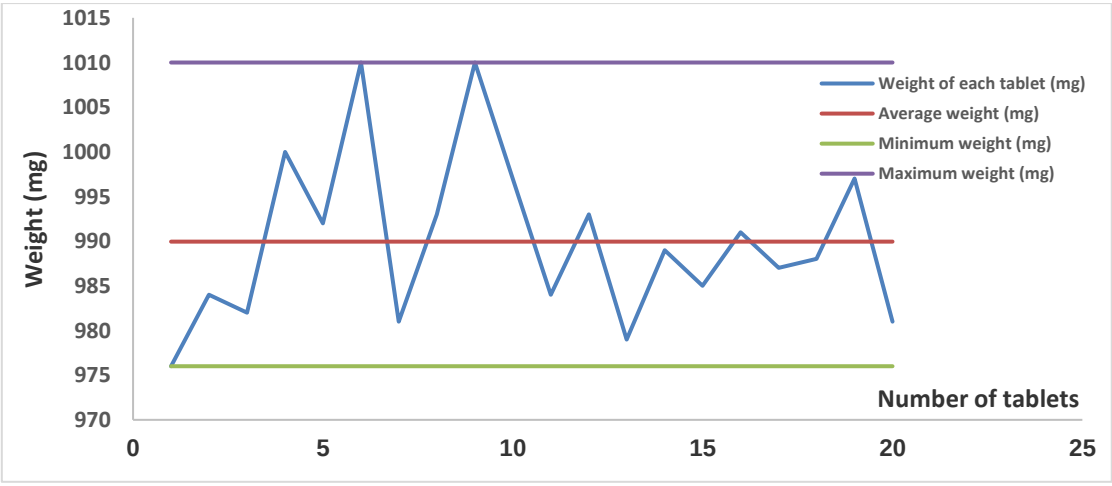

Figure 3: Weight variation test of MET-2 (oblong-shaped metronidazole tablets)

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Hardness test: Compared to oblong tablets, round tablets are more likely to break because they are under greater stress. This pattern is understandable based on the hardness readings for metronidazole round and oblong-shaped tablets provided in **Figure 4**. In the present study, all the brands of metronidazole showed a deviation from the force range (4.0-6.0 kg/cm^2) which is the minimum crushing force requirement for a satisfactory tablet as per the USP compendial range [22]. Therefore, the two brands failed to meet the manufacturer's requirement for hardness. The MET-2 brand showed comparatively higher hardness than the MET-1 brand. Tablet hardness is mostly based on the materials used, the binder type and concentration used in a formulation, the ratio of tablet height to diameter, the extent between the upper and lower punches at the moment of compression, as well as the pressure used (compression force) [5, 22]. There is a linear relationship between compression pressure and tablet hardness [23]. Therefore, the oblong shape of the metronidazole tablets is subject to higher compression pressures than the round-shaped tablets and will require more compression pressure to break than the round-shaped tablets due to their higher hardness value [8].

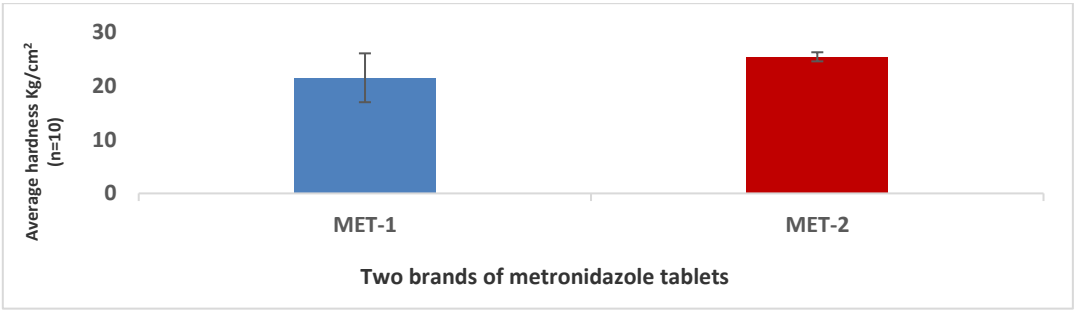

Figure 4: Comparison of the MET-1 and MET-2 tablet hardness tests

The friability has experimentally been determined for different-shaped metronidazole tablets. The tablet formulation is acceptable if the friability is less than 01.0% as per the USP requirements. As the friability values for MET-1 and MET-2 were close to zero, they satisfied the USP friability requirements. This indicates that the two brands are mechanically stable which may be connected to the film coat that surrounds the tablets, and that they will not undergo any mechanical shocks or abrasions during the manufacturing, packing, and transportation processes [16, 22]. The disintegration of tablets of varying shapes was observed by testing to identify the form that has the biggest influence on the disintegration time. **Figure 5** provides the shape and the disintegration time. Film-coated tablets are designed to disintegrate in 30 min according to USP requirements [5]. Here, the disintegration time of metronidazole film-coated tablets, MET-1 and MET-2, was found to be less than 10 min, satisfying the requirement. The study's experimental results indicate that the oblong-shaped metronidazole tablets have a greater disintegration time than the round-shaped tablets; hence, the round-shaped tablets would dissolve more quickly than the oblong-shaped ones due to the oblong shape of the metronidazole tablets is subject to higher compression pressures than the round-shaped tablets. The disintegration time is directly proportional to the compression pressure [23].

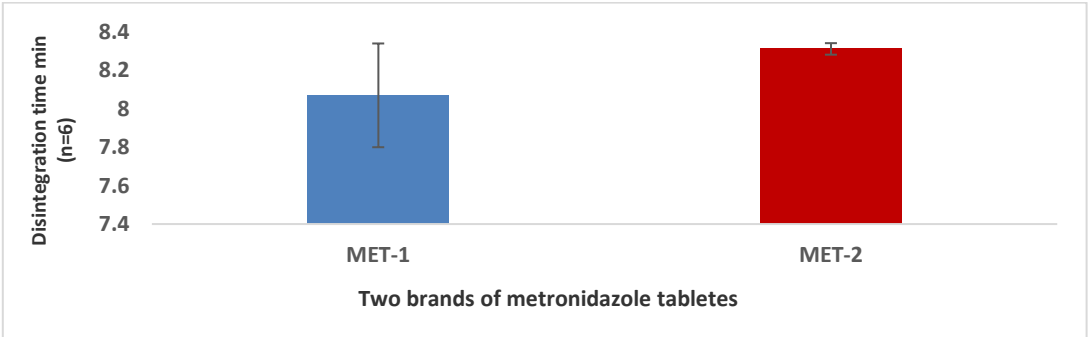

Figure 5: Comparison of the metronidazole MET-1 and MET-2 tablet disintegration tests

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The drug content of round and oblong metronidazole tablets was not affected by variations in shape whereas the results of the drug content test of MET-1 and MET-2 showed a potency range of 90.0-110.0% of the labelled quantity of metronidazole and complied according to USP requirements [5]. **Figures 6 and 7** illustrate the drug content of MET-1 and MET-2, respectively. The findings indicate that the upper limit is equal for both brands, but the lower limit of the oblong-shaped metronidazole tablets is higher than the lower limit of the round-shaped tablets. Although MET-2 has a weight greater than MET-1, its percentage drug content it is within the range specified by the USP [23].

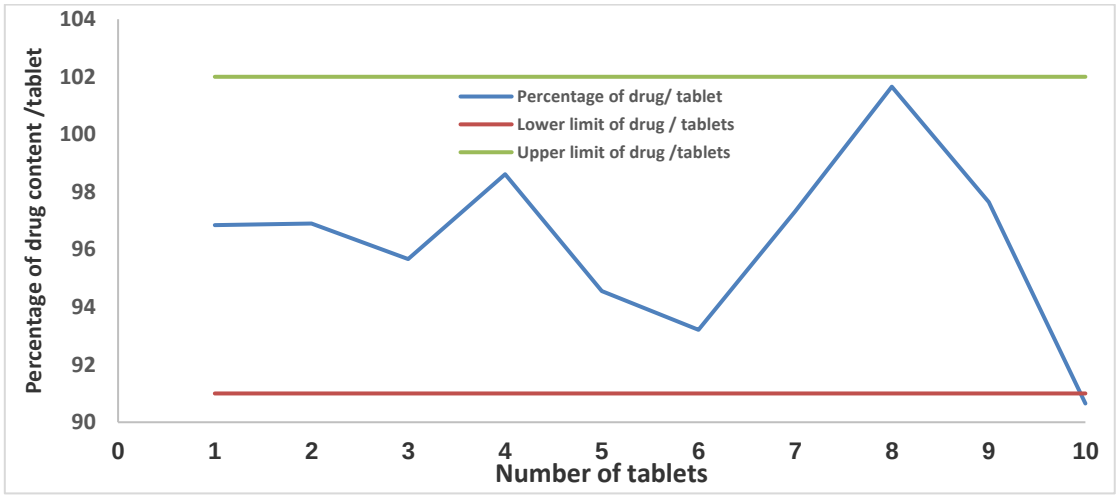

Figure 6: Percentage of drug content of MET-1 round-shaped metronidazole tablets

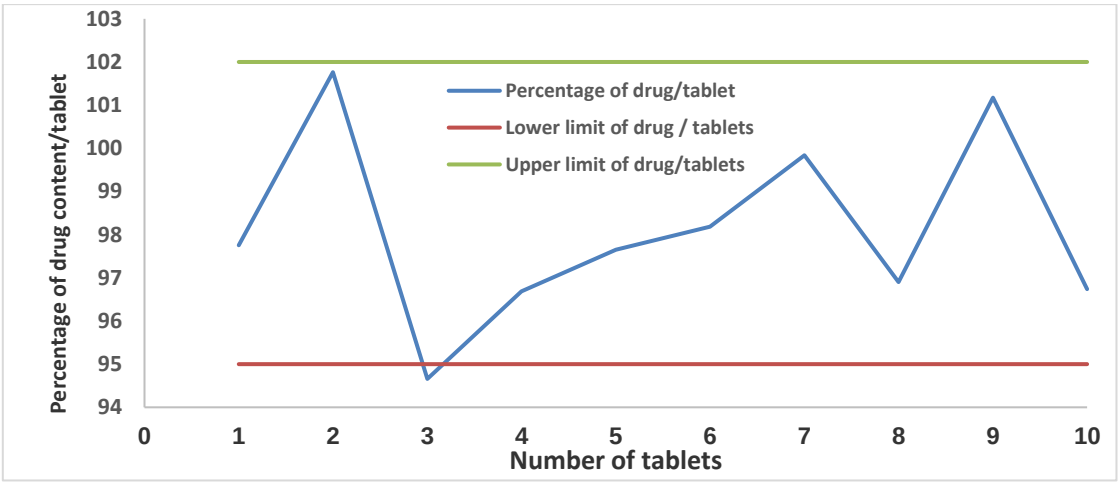

Figure 7: Percentage of drug content of MET-2 oblong-shaped metronidazole tablets

Figure 8 illustrates the percentage of drugs released from each shape of metronidazole tablet. According to USP specifications for metronidazole film-coated tablets, the release of the drug should not be less than 85.0% of the labelled amount in 60 min [16]. The two brands had satisfactory results from the dissolution test. After 15 min, brand MET-2 exhibited the most drug release, while brand MET-1 showed the slowest drug release rate. The oblong-shaped metronidazole tablet showed a slightly greater dissolution rate than the round-shaped tablet, but there was no apparent variation in the dissolution profile.

Mechanisms of drug release are complicated processes that involve swelling, erosion and diffusion across tablet surfaces; compression force and hardness might not have a major impact on these processes [23]. In the current study, the pharmaceutical quality parameters have been assessed for two different metronidazole tablet brands marketed in Libya, and the impact of tablet shape on the quality of tablets was evaluated, but the

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manufacturers of the two brands failed to produce tablets with good crushing strength (hardness values were found to be quite high as compared to the permissible limit). Based on the study of the two shapes of metronidazole brands, it was found that brands MET-1 and MET-2 are more closely pharmaceutically equivalent and exhibit highly similar behaviours in quality tests. The design of various metronidazole tablet shapes may be due to patient compliance and the attractive appearance of tablets for marketing purposes. Thus, pharmacists advise using these brands interchangeably without worry due to the difference in shape. However, additional studies are needed on the significance of tablet shapes would be beneficial, as the current study is dependent on a limited sample of tablet shapes and brands.

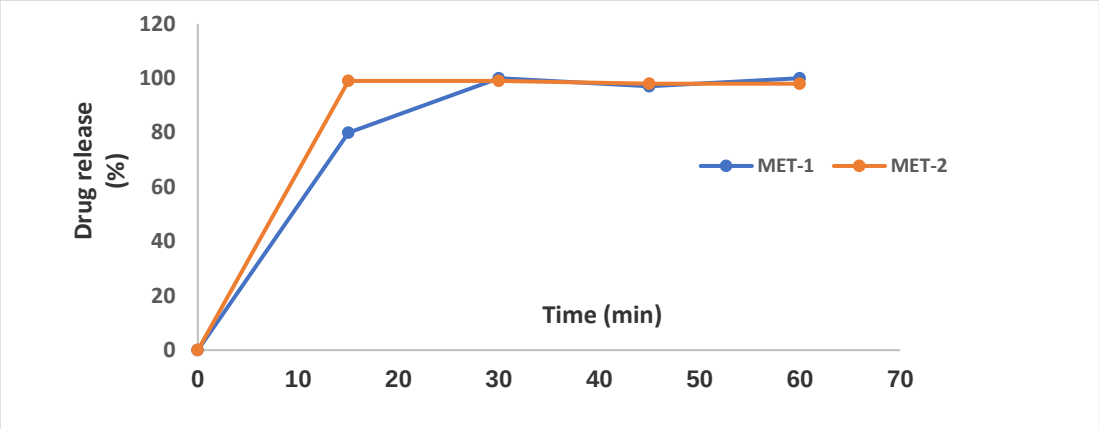

Figure 8: Dissolution profiles of the MET-1 and MET-2 brands of metronidazole tablets

Conclusion: The findings of weight variation, content uniformity, friability, disintegration time and dissolution tests of the two marketed products of metronidazole comply with the USP limit. The variations in the shape of metronidazole tablets have no impact on the quality of the marketed brand of metronidazole in Libya.

References

1. Ugurlu T (2017) Mini tablets: A short review-revision. Open Journal of Chemistry. 3 (1): 012-022. doi: 10.17352/pjmcr.000007
2. Kadiri MS, Michrafy A (2013) The effect of punch's shape on die compaction of pharmaceutical powders. Powder Technology. 239: 467-477. doi: 10.1016/j.powtec.2013.02.022
3. Augsburger LL, Hoag SW (2008) Pharmaceutical dosage forms: Tablets. 2: 1552. 3rd ed., CRC Press, Boca Raton. ISBN: 9780429191794. doi: 10.1201/b15115
4. Davies PN, Worthington HEC, Podczeck HE, Newton JM (2007) The determination of the mechanical strength of tablets of different shapes. European Journal of Pharmaceutics and Biopharmaceutics. 67 (1): 268-276. doi: 10.1016/j.ejpb.2007.01.014
5. Noor S, Salam BAF, Hima HN, Bhuiyan MSI, Chowdhury S (2017) Comparative *in-vitro* quality evaluation of some brands of metronidazole tablet available in Bangladesh. International Journal of Applied Research. 3 (7): 753-758. Corpus ID: 54907169.
6. US Food and Drug Administration (2022) Size, shape and other physical attributes of generic tablets and capsules: Guidance document. U.S. Food and Drug Administration. FDA-2013-N-1434.
7. Molavi F, Hamishehkar H, Nokhodchi A (2020) Impact of tablet shape on drug dissolution rate through immediate released tablets. Advanced Pharmaceutical Bulletin. 10 (4): 656-661. doi: 10.34172/apb.2020.079
8. Nisar H, Khan SA, Alossaimi MA, Abbas M (2022) Effect of shape on physico-chemical properties of metronidazole tablet. Brazilian Archives of Biology and Technology. 65: 1-9. e22210611. doi: 10.1590/1678-4324-2022210611
9. Vinay S, Sudeendra BR, Balamuralidhara V, Pramod KTM (2011) Comparative study of in-process and finished products quality control tests of IP, BP & USP for tablets. International Journal of Pharmacy Teaching and Practices. 2 (4): 176-183. doi: Nil.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

10. Kumar TNP, Ram PS, Nannepamu PB, Nagabhushanam MV, Ramakrishna G, Bonthagarala B, Sindhu BYR, Kumar Ch S (2022) A review on in process and finished products quality control tests for tablets according to pharmacopoeias. Indo American Journal of Pharmaceutical Sciences. 9 (5): 29-36. doi: 10.5281/zenodo.6522026
11. Siddappa F, Mallikarjun M, Reddy PT, Tambe M (2008) Spectrophotometric determination of metronidazole through Schiff's base system using vanillin and PDAB reagents in pharmaceutical preparations. Ecletica Quimica. São Paulo. 33 (4): 41-46. doi: 10.1590/S0100-46702008000400005
12. Elghnimi TY, Ammar AA, Saadawi SS, Algeryani AM (2021) Pharmaceutical evaluation of some commercial brands of metronidazole 500 mg tablets marketed in Tripoli, Libya. International Journal of Science and Research. 10 (12): 97-104. doi: 10.21275/SR211130012431
13. Bayoumi AA, Fattah H, Rasoul SA, Rasoul MA, Jawad E (2019) Comparative in-vitro pharmaceutical evaluation of some selected brands of metronidazole tablets marketed in Iraq. International Journal of Pharmaceutical Science and Research. 4 (2): 13-15. doi: Nil.
14. Almdaaf MA, Altriki MS, Elnekaib MA (2023) Post-marketing quality assessment of paracetamol brands in the Libyan market. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 3 (4): 73-79. doi: 10.5281/zenodo.10289340
15. Eteer SA, Elbakay JA, Almashai NA, Maree HA, Elgadi SS, Almog TK (2023) A comparative evaluation of furosemide tablet marketed in Libya. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 3 (4): 83-89. doi: 10.5281/zenodo.10389843
16. Al-Naimi R, Khan S (2014) Comparative *in-vitro* pharmaceutical evaluation of four brands of metronidazole tablets marketed in gulf region. Jordan Journal of Pharmceutical Sciences. 7 (2): 144-152. doi: Nil.
17. Saffaj T, Charrouf M, Abourriche A, Abboud Y, Bennamara A, Berrada M (2004) Spectrophotometric determination of metronidazole and secnidazole in pharmaceutical preparations. Il Farmaco. 59 (10): 843-846. doi: 10.1016lJ.FARMAC.20040060001
18. Rahman M, Jahan FI, Fahim NF, Paul N, Jahan N, Tanny SZ (2020) *In vitro* comparative quality evaluation of leading brands of metronidazole tablets available in Bangladesh. Pharmacology Online. 2: 63-72. Corpus ID: 236907259.
19. Aleanizy FS, Al-Eid H, El Tahir E, Alqahtani F, Al-Gohary O (2017) Stability and in vitro dissolution studies of metronidazole tablets and infusions. Dissolution Technology. 24 (2): 22-27. doi: 10.14227/DT240217P22
20. Wilkins CA, Hamman H, Hamman JH, Steenekamp JH (2024) Fixed-dose combination formulations in solid oral drug therapy: advantages, limitations, and design features. Pharmaceutics. 16 (2): 178. doi: 10.3390/pharmaceutics16020178
21. O'Connor T, Lee S (2017) Emerging technology for modernizing pharmaceutical production: Continuous manufacturing. Developing solid oral dosage forms. Pharmaceutical Theory and Practice. 2nd ed., 1031-1046. Elsevier Inc. doi: 10.1016/B978-0-12-802447-8.00037-6
22. Majeed SM, Al-Shaheen MK, Al-Zidan RN (2021) Quality control study on conventional metronidazole tablets available in the Iraqi market. Research Journal of Pharmaceutical Technology. 14 (2): 803-808. doi: 10.5958/0974-360X.2021.00141.4
23. Adeleye O (2019) Relationship between compression pressure, mechanical strength and release properties of tablets. Polymers in Medicine. 49 (1): 27-33. doi: 10.17219/pim/111888

Author contribution: AMA conceived and designed the study. WMA, AMA & DMS contributed to data collection, data analysis, interpreted data and drafted the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.