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Comparative *In-vitro* pharmaceutical evaluation of some selected brands of metronidazole tablets marketed in Iraq

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Abstract
Objective: The aim of this study was to assess the quality of some selected metronidazole products in community pharmacies in Iraq
Methods: Different parameters of quality control of pharmaceutical products can guarantee the quality and bioavailability and optimal therapeutic activity. Used quality control parameters, i.e., the variation of weight, friability, content uniformity, disintegration time and dissolution profiles were tested *in vitro*.
Results: The weight range was 0.79-0.82 g, 0.74-0.78g, 0.82-0.86g, 0.95-0.97g, 0.63-0.72 g 0.62-0.65 g for Neogyl, Anaerobex, Metrobac, Negazole, Flazi-MD and Metrosule, respectively. Disintegration time was 11 min,5 min, 43 min, 7 min, 30 min, 12 min for Neogyl, Anaerobex, Metrobac, Negazole, Flazi-MD and Metrosule, consequently. Content uniformity was satisfactory and dissolution rate of all brands was more than 85% after 60 min except Anaerobex and neogyl whose dissolution rate was 83.06% and 80.22%.
Conclusion: The results showed that all products fulfill the given specification of Pharmacopeia (USP-NF) which its dissolution rate was less than % in USP (85% after 60 min) except Anaerobex and neogyl. Disintegration of Anaerobex showed the quickest disintegration while Metrobac represented the slowest.

Keywords: metronidazole, quality control evaluation, hardness, dissolution

Introduction
Metronidazole (2-methyl-5-nitroimidazole-1-ethanol) is an oral synthetic metronidazole antibiotic medication used for the treatment of infections caused by anaerobic bacteria and protozoa [1]. It is an antibiotic, amebicide, and antiprotozoal [2] and it has structural formula:

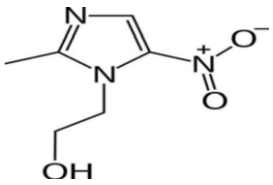

Fig 1: Chemical structure of metronidazole

Some of metronidazole brands are manufactured in Iraq and others are imported from other parts of the world. Various brands available in the market are considered pharmaceutically equivalent if they contain the same amount of active ingredient in the identical dosage form and meet the same compendial or other applicable standards but may differ in characteristics such as shape, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling requirements [3] It is the joint responsibility of the manufacturers and the drug law enforcing agencies to ensure that various marketed pharmaceutical products containing the same active ingredient in the identical dosage forms are uniform, safe and effective. The safety and efficacy of drug products can be guaranteed when their quality is reliable and is reproducible from batch to batch. To ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product. Metronidazole is one of the commonly used amoebicidal drug in clinical practice for the treatment of amoebiasis and giardiasis, therefore, it is necessary to monitor and ascertain the quality of the various brands available in the market. The quality i.e. safety and efficacy of immediate release oral solid dosage form such as tablets can readily and satisfactorily be assessed by carrying out dissolution studies and *in- vitro* pharmaceutical tests. The present study was carried out to investigate and assess the pharmaceutical quality of six different brands of Metronidazole 500 mg tablets marketed in Iraq using *in vitro* methods as per the USP and unofficial standards as recommended by the manufacturers to emphasis that all brands are pharmaceutically equivalent. The assessment of tablets included the evaluation of weight uniformity, disintegration time, dissolution rate and chemical assay by UV spectrophotometric method to determine the content of active pharmaceutical ingredient (API) [4]. friability, crushing strength/hardness were not performed because of all these products are film coated

Materials and Methods
Materials
Hydrochloric acid was supplied by Ibn Hayyan University College, Karbala, Iraq.

Marketed film coated tablets products
Anaerobex 500mg tablets, G.L. Pharma Gmbh, Austria, lot: 6L200A, manufacture date: 11-2018, expire date:11-2021, Neogyl 500mg tablets, Neopharma, United Arab Emirates,

batch number: NZ017009, Manufacture date:7/2017, expire date:7/2020, Metrosule 500mg tablets, Ajanta, India, lot:AD/083, manufacture date: 11/2017 and expire date:11/2020, Flazi- MDI 500 mg, Modern pharmaceutical, Iraq, manufacture date:3-2017 and expire date:3-2020, Negazole 500 mg Julphar, United Arab Emirates, manufacture date: 4-2018 expire date:4-2021 and Metrobac 500mg Alfayhaa pharmaceutical, Iraq, batch No. 5, manufacture date:11/2016 and expire date: 11-2019.

Analytical Method

Accurately weighed metronidazole was dissolved in 0.1 N HCl in a 100 ml volumetric flask. From the stock solution, different dilutions were prepared to draw a calibration curve by measuring absorbance using UV spectrophotometer (UV-Spectrophotometer AVI-2700, labtech, Ined) from 200-400 nm. The concentration of metronidazole was calculated using the linear regression equation of the calibration curve.

Construction of calibration curve in 0.1 N HCL

A weight of metronidazole was accurately weighed (equivalent to 500 mg metronidazole) and transferred into 100 ml volumetric flask, 50 ml 0.1 N HCl, was added and shaken to dissolve, completed to the volume using 0.1 N HCl, mixed well then diluted to give serial concentrations of metronidazole in the range of 5-40 µg/ml in 0.1 N HCl, filtered, scanned in the range of 200-400 nm (UV system in the range of 200-400 nm with 1 cm matched quartz cells) using 0.1 N HCl as a blank and λ 296 nm was chosen to be the maximum λ_{max} and the calibration curve was constructed

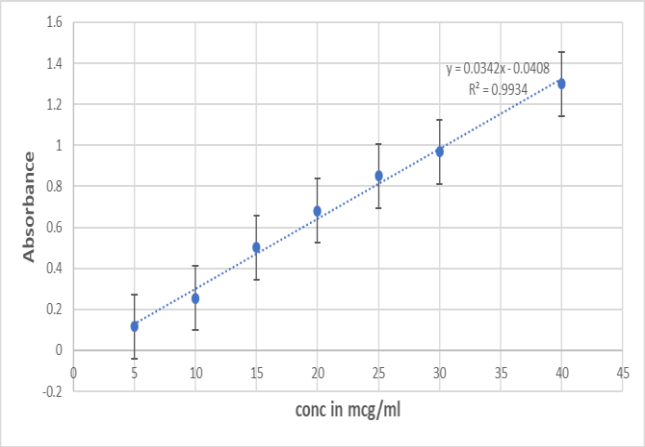

Fig 2: Graph representing calibration curve of metronidazole in 0.1 N HCl. Error bars represent standard deviation of the mean (±standard deviation)

Evaluation tests for the selected products

Weight variation

For each brand, ten tablets were randomly selected and weighed individually using an analytical balance (Electronic balance, China). The average weights were calculated and the percentage deviations from mean values were calculated. Then the standard deviation, and percentage of related standard deviation (RSD) was determined [5].

Assay

The quantity of metronidazole was determined in each product according to USP. 10 tablets were weighed and average weight was found out, a weight equivalent to 100 mg of metronidazole was transferred into 100 ml volumetric flask, 50 ml of 0.1 N HCl. Serial dilution was done and measure at 296 nm with the UV spectrophotometer. The amount of metronidazole in each product was calculated using the equation of the calibration curve.

Hardness test

Tablet hardness is defined as the force required breaking the tablet in a diametric compression test. If the tablet is too hard, it may not disintegrate in the required period of time to comply with the dissolution specification. Conversely, the hardness must not be so low that the tablets are soft and friable. To get a satisfactory quality tablet hardness should be between 4 and 8 kg 6. The results of the branded products (Table 2) for the hardness test were satisfactory type hardness tester (YD-2/ Guoming, China).

Disintegration time test

The disintegration helps the formulator in the preparation of a satisfactory tablet formula as a control test on the process. Therefore, to ensure batch-to-batch product uniformity, DT test is very important.

Disintegration apparatus (ElBJ, Guoming, China) containing six glass tubes that are three inches long, open at the top and are held against a 10-mesh screen in the lower end of the unit basket rack was used in the study. For the test, a tablet was placed in each tube and the frame of the basket was placed in a beaker containing 1 liter of distilled water to 37^0C, such that the tablets remain below 2.5 cm the surface of the media in its upward movement and descent no closer than 2.5 cm from the bottom of the beaker. The disintegration time of each tablet was determined and the average time was calculated [5].

Content uniformity

The uniformity of content was determined by crushing ten tablets from each formula and determining the drug content of each tablet individually using the developed method [5].

***In vitro* dissolution rate studies**

The dissolution studies were carried out according to the USP paddle method. The stirring rate was 50 rpm at 37 ±0.5 °C. The dissolution medium was 900 ml of 0.1 M HCl [5]. The samples (n= 12) were at ten minute intervals withdrawn at 15, 30, 45 and 60 minutes and assayed spectrophotometrically at 296 nm. The percent of cumulative drug dissolved of each tablet was determined using the linear regression equation of the calibration curve.

Results and Discussion

The weight range was 0.79-0.82 g, 0.74-0.78g, 0.82-0.86g, 0.95-0.97g, 0.63-0.72 g 0.62-0.65 g for Neogyl, Anaerobex, Metrobac, Negazole, Flazi-MD and Metrosule, respectively. Disintegration time was 11 min,5 min, 43 min, 7 min, 30 min, 12 min for Neogyl, Anaerobex, Metrobac, Negazole, Flazi-MD and Metrosule, consequently. Content uniformity was satisfactory and dissolution rate of all brands was more than 80% after 30 min While Negazole showed the most rapid release 97.6% after 15 min and Metrobac showed the lowest release after 15 min. The results are shown below in table 1 and 2.

Table 1: Weight variation Measurement (n = 10)

brand	Minimum weight(g)	Maximum weight(g)	Average weight (g)	Standard Deviation (SD)	%Relative Standard deviation (RSD)
Neogyl	0.79	0.82	0.80	0.008433	1.048881
Anaerobex	0.74	0.78	0.76	0.01075	1.403394
Metrobac	0.82	0.86	0.84	0.012293	1.459976
Negazole	0.95	0.97	0.96	0.007379	0.767846
Flazi- MDI	0.63	0.72	0.68	0.024698	3.584615
Metrosule	0.62	0.65	0.63	0.009661	1.519025

Table 2: Results of quality tests

Brands	Assay* (%)	Content uniformity* (%)	Disintegration time* (min)	Average drug release after 60 min* (%)
Neogyl	100.5%± 0.2	99.6%± 0.2	11±0.3	80.32± 0.1
Anaerobex	99.1%± 0.1	98.7%± 0.3	5±0.4	83.06± 0.1
Metrobac	99.5%± 0.2	98.6%± 0.2	43 ±0.5	97.58± 0.1
Negazole	99.7%± 0.3	100.7%± 0.2	7 ±0.1	99.68± 0.1
Flazi- MDI	98.6%± 0.2	99.7%± 0.3	30 ±0.4	89.84± 0.1
Metrosule	98.9%± 0.1	98.3%± 0.2	12 ±0.2	97.74± 0.1

*All values are reported as mean ± standard deviation (SD), n=6.

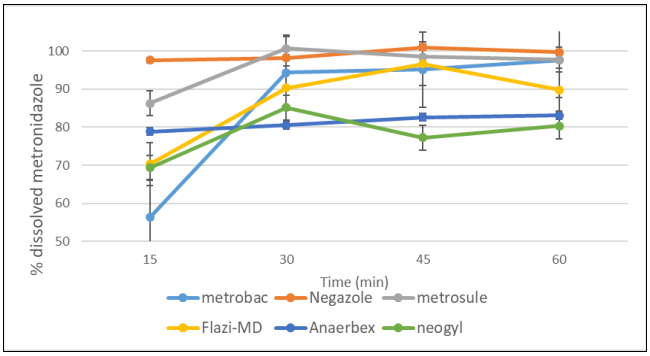

Fig 3: Dissolution profile of metronidazole from tablets (values represent mean ±SD, n=6)

Conclusion

The results showed that all products fulfill the given specification of Pharmacopeia (USP-NF) which its dissolution rate was less than % in USP (85% after 60 min) except except Anaerobex and neogyl tablets. Disintegration of Anaerobex showed the quickest disintegration while Metrobac represented the slowest

Conflicts of interest

The authors declare there is no conflict of interest.

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