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COMPARATIVE *IN-VITRO* EVALUATION OF SOME COMMERCIAL BRANDS OF METFORMIN TABLETS MARKETED IN TRIPOLI-LIBYA

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ABSTRACT
The availability of several brands of Metformin tablets in Libyan pharmacies today places health practitioners in a problem of generic substitution. The aim of the present study was the evaluation and comparison between six different Metformin 500 mg brands, which are commercially available in the Libyan market produced by various pharmaceutical companies with different trade names. The physicochemical equivalence of six brands of Metformin tablets were investigated through the evaluation of both official and non-official standards according to the British Pharmacopoeia including uniformity of weight, thickness, hardness, disintegration time, drug content as well as dissolution rate. Acceptable external features as well as uniformity in diameter and thickness revealed for all the tablets. The entire brands complied with the official specifications for uniformity of weight where no tablet showed a deviation more than ±5%. Brands B, C, F had the highest crushing strength and highest disintegration time compared to the other brands. All the Six brands could be regarded as bioequivalent and therefore can be interchanged in the clinical practice. This sort of study is good indicator for the evaluation of the idealness of commercial products.

KEYWORDS: Metformin, physicochemical properties, evaluation, bioequivalence.

1. INTRODUCTION
Many brands accessible 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 compendia or other applicable standards (i.e strength, quality, purity and identity), but may vary in characteristic such as shape , packaging , excipients (including colors, flavors, preservatives) expiration date etc.[1] Regular laboratory tests of drugs in the market are crucial to maintain the quality of drugs, especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services.[2]

Quality control procedures, which are useful tools for batch to batch consistency in manufacturing, should be performed for every drug product. Drug has more than three generic products require analysis for their biopharmaceutical and chemical equivalency. These methods ensure that any of the generic products can be used interchangeably.[3]

Evidences point to the fact that different products with the same amount of active ingredient have shown distinct differences in their therapeutic effects.[4,5] This possibly due to difference between the purity of active ingredients, type of excipients, proportion between them and manufacturing variables such as mixing method and granulation procedures as well as coating parameters.[6]

Drug products that are bio-pharmaceutically and chemically equivalent must be identical in their quality, strength, purity and active ingredient release profile. They must to be in the same dosage form and intended for the same route of administration.[7] Dissolution testing of drug product is an important criterion in assessing the quality control to monitor batch to batch consistency of drug release.[8] The variations in the drug release among some generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution rate determination used also for prediction of *in-vivo* bioavailability in most oral preparations and the rate of absorption.[4,9] Dissolution test is a surrogate marker for bioequivalence tests as it is a practical and economical approach in developing countries where technology and resources are limited for *In-vivo* study.[10] In the dissolution study, the release of active pharmaceutical ingredient of drug product for the dissolution medium that is comparable to gastrointestinal tract fluid is determined. Based on this, *in vitro* dissolution may be important in assessing *in-vivo* performance of drug absorption.[3,11]

The active pharmaceutical ingredient is the chemical that has the desired biological effect. There may be many ingredients in a tablet, for example diluents, binders, disintegrants, thickening agents, glidants, colorants, sweetening agents, but the API is the ingredient concerned for the therapeutic effectiveness. Most dosage forms are designed to deliver the API to the site of action.[12] It is important to know if there are variations in the percentage content of active ingredients. This can be detected through an assay test. The percentage content of active drug should be routinely measured to check whether a tablet contains a proper amount of drug.[13]

Manufacturing methods and the excipients used in the production processes could contribute to the quality and release skillfulness of medicament. Therefore, to ensure the requisite quality, drug manufacturers are required to examine their products during and after manufacturing and at various intervals during the shelf life of the product.[14]

Metformin hydrochloride is an oral anti-diabetic drug from the biguanide class used mainly to treat type 2 diabetes mellitus, works by improving the body's sensitivity to insulin, allowing it to use glucose in the normal way. It is the first line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function. Metformin hydrochloride is also being used increasingly in polycystic ovary syndrome (PCOS) which is a syndrome of ovarian dysfunction and hyperandrogenism.[15] Chemically known as N,N-dimethylimidodicarbonimidic diamide, is freely soluble in water, but has low permeability to cell membranes. Therefore, it can be classified as a BCS class III drug.[16]

The increase level of use of Metformin tablets in clinical practice creates the need to monitor and ascertain the quality of the various brands available in the drug market for quality control assessment and for purpose of generic substitution.

The present study has been undertaken to evaluate and compare various quality control parameters along with dissolution profile of six marketed metformin tablet brands prior to determining their interchangeability. Drug should be regularly checked to ascertain that their quality meet the standards and to identify counterfeits, where nowadays, drugs can be obtained from more than one source and might be chance of presence of some superiors along with sub-standard drugs, that makes the patients conscious about the selection of safety, effective as well as economical medicine.

2. MATERIALS AND METHODS

Metformin Hcl tablets having label strength of 500 mg of six different brands were purchased from local pharmacies in Tripoli Libya. The products were coded as A, B, C, D, E and F as illustrated in Table (1) and the study was performed within product expiration dates.

Hydrochloric acid, potassium bromide, absolute ethanol, potassium dihydrogen orthophosphate, sodium hydroxide, and freshly prepared distilled water were used throughout the work. Six different brands of Metformin Hcl 500mg tablet were obtained from different community pharmacies.

Table 1: Label information of six different brands of Metformin tablet 500mg under investigation.

Product code	Batch No.	Manufacture Date	Expire Date
A	893	12\2011	12\2016
B	DS3819	7\2013	7\2016
C	JC4040	Not available	5\2017
D	48058	6\2014	5\2019
E	280755	9\2013	8\2018
F	BUH034156	Not available	11\2018

2.1 Visual Inspection

The general appearance of tablets, their visual identity and overall elegance are essential for consumer acceptance.[17] Samples of 20 tablets from each brand were randomly selected and unpacked to inspect for their external characters such as color, shape, size, presence of grooves, monograms and surface defects.

2.2 Uniformity of Weight

Samples of 20 tablets from each of the 6 brands were randomly selected; their individual weights were measured and recorded using sensitive digital balance, (Sartorius AG Gottingent). The average weight of each sample was calculated and the deviation of each tablet weight from the average weight was determined in percent.[18] Acceptable deviation are not to be more than ± 5%.[19]

2.3 Hardness Test

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength.[18] The hardness, thickness, and diameter of samples of 10 tablets were determined using tablet combination tester (Erweka TBH 320 WTD Multi-Check tester, Germany). In the hardness test, pressure was applied on the tablet and the force caused the tablet to break up was recorded. The values were expressed in Kg/cm^2.

2.4 Disintegration Test

The disintegration time of randomly selected six tablets of each of the six brands was determined at 37^0C in distilled water using (Pharma test) disintegration tester apparatus according to BP specifications. The basket was raised and lowered at a fixed frequency of 30 cycles / min. The disintegration time was taken to be the time no particle of any tablet was left on the basket. The average disintegration time was recorded.

2.5 Dissolution Rate Determination

Dissolution is defined as the amount of substance that goes into solution per unit time under standardized conditions of liquid/ solid interface, solvent composition and temperature.[20] Dissolution test was carried out on six different brands of Metformin tablets (500 mg). Dissolution rates were determined using tablet dissolution apparatus (pharma test type PT-dT70). One tablet was put in each of the compartments of the apparatus using 900ml of phosphate buffer pH 6.8, at 37 ±0.5 ^{0}C. The basket was rotated at 100 rpm. Ten milliliters of sample was drawn at intervals of 10, 20, 30, 45 and 60 minutes. A fresh 10 ml dissolution medium was replaced after each sampling. Each of the withdrawn sample was filtered, the filtrate diluted and the its absorbance was measured at λ max 233 nm using UV visible spectrophotometer, then the concentration of Metformin hydrochloride in the samples was calculated according to metformin monograph in the BP.

2.6 Assay of Metformin Tablets

The test for assay is done to determine the actual amount of the active ingredient present in the tablet and it is the same as the labeled amount. Initially 20 tablets were weighed and average weight was taken. Tablets were then powdered using mortar and pestel. Powder equivalent to 0.1g of Metformin HCl was then stirred with 70 ml of distilled water for 15 minutes. The result solution was diluted to 100 ml with distilled water and filtered. The filtrate was then suitably diluted and absorbance of the final solution was measured by UV-visible spectrophotometer, taking 798 as the value of A (1%, 1cm) at the maximum at 232nm.

2.7 Identification

For identification according to BP specification a quantity of the powdered tablets, containing 20 mg of Metformin HCl, was mixed with 20 ml of absolute ethanol, filtered, evaporated to dryness and the residue was dried at 105 ^{0}C for 1 hr. infrared spectra were recorded for obtained residue

3. RESULTS AND DISCUSSION

Table (2) shows the visual inspection of tablets, evidence of physical instability demonstrates that tablets were undamaged, smooth, and usually uniform in color. Table (3) shows the evaluated physicochemical parameters; all investigated brands were within their shelf life at the time of study. Six different brands of Metformin tablets obtained from different pharmacies within Tripoli were subjected to a number of pharmacopoeial tests in order to assess their biopharmaceutical equivalence. The assessments involved the evaluation of uniformity of weight, hardness, disintegration and dissolution as well as chemical content determination. The uniformity of weight determination for all the brands gave values which complied with official book specifications for weight uniformity as none of the brands deviated by up to ± 5% from the mean value.

Crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It is a property of a tablet that is measured to assess its resistance to permanent deformation. The result indicates that all brands passed the test while brand B, C, F had the highest crushing strength of all the six brands. Thickness and diameter are non pharmacopoeial requirements but naturally they will have an effect on packaging[21] as well as they are used in calculation of tensile strength of tablets.[22] The rate of disintegration is directly proportional to the rate of dissolution. The rate of disintegration is influenced by the rate of influx of water into the tablets. The results showed that all the brands passed the disintegration test according to the pharmacopeia which specifies 30 minutes for film coated tablets. The dissolution test according to BP required that not less than 70% of the active ingredient should dissolve within 45 minutes. All the tested brands have satisfied this requirement. The results obtained from the study revealed that all the brands passed the general standard specifications for dissolution rate test for conventional release tablets. The difference in the result can be correlated to all factors which affect the dissolution rate from the raw material (purity) which can affect solubility, and all diluents which were used in the formulation of each brand.[23] All samples analyzed fall within the acceptable limit of 95% to 105% assay. A sample of the obtained FTIR spectra is shown in Figures (1, 2, 3, 4, 5, 6 and 7) thus the substance present in each of the tested tablets was positively identified as Metformn HCl.

Table 2: Appearance features of the different brands of Metformin 500mg tablets.

Parameter	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
Shape and color	Round, White	Round, White	Round, White	Round, White	Round, White	Round, White
Surface texture and Convexity	Smooth, Convex surface	Smooth, Convex surface	Smooth, Convex surface	Smooth, Convex surface	Smooth, Convex surface	Smooth, Convex surface
Monograms and score lines	None	Yes	Yes	None	None	Yes

3.1 Physicochemical Properties of Metformin Tablets

Weight variation, hardness, disintegration time, dissolution percentage, assay percentage as well as thickness and diameter are shown in Table (3).

Table 3: Evaluated physicochemical parameters of the six brands of Metformin tablets.

Brands	Average weight g	Dissolution %	Hardness (kg/cm^2)	Disintegration time (min)	Assay (%)	Diameter (mm)	Thickness (mm)
A	637.50 ± 8.82	91.85	9.938 ± 1.022	5	95.11	12.71 ± 0.02	5.20 ± 0.04
B	521.20 ± 4.05	88.82	32.158 ± 1.453	9	96.35	11.08 ± 0.03	5.69 ± 0.03
C	584.36 ± 18.43	80.49	40.908 ± 4.814	8	95.02	11.04 ± 0.04	6.06 ± 0.15
D	554.54 ± 3.19	88.11	18.943 ± 1.343	7	101.1	12.00 ± 0.16	4.60 ± 0.02
E	529.81 ± 5.28	89.77	17.831 ± 1.274	6	95.1	11.97 ± 0.03	5.03 ± 0.03
F	591.82 ± 7.76	86.67	27.913 ± 2.494	14	99.12	11.11 ± 0.02	5.81 ± 0.05

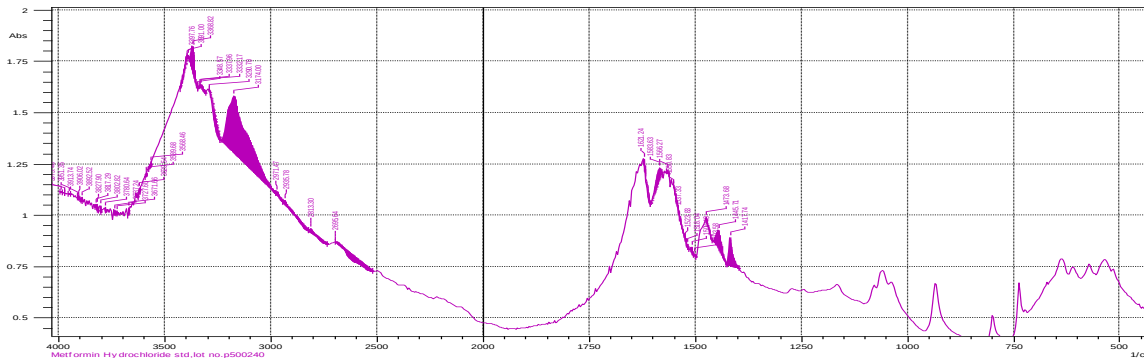

Figure 1: FTIR spectra of Standered Metformin.

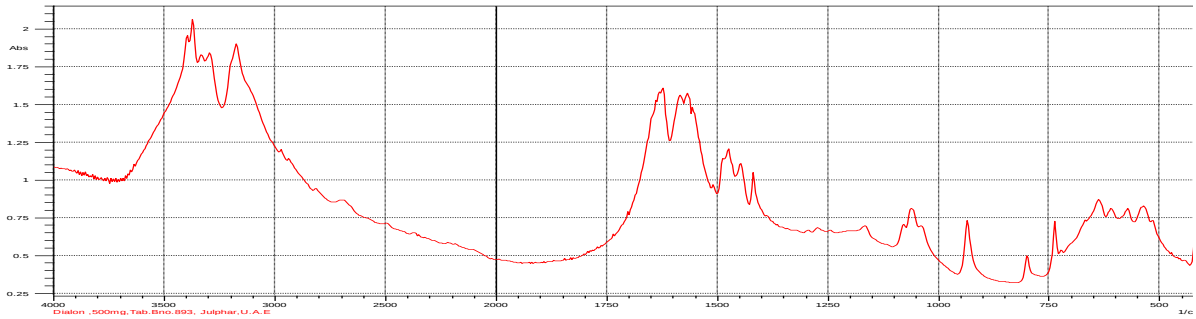

Figure 2: FTIR spectra of Brand A Metformin.

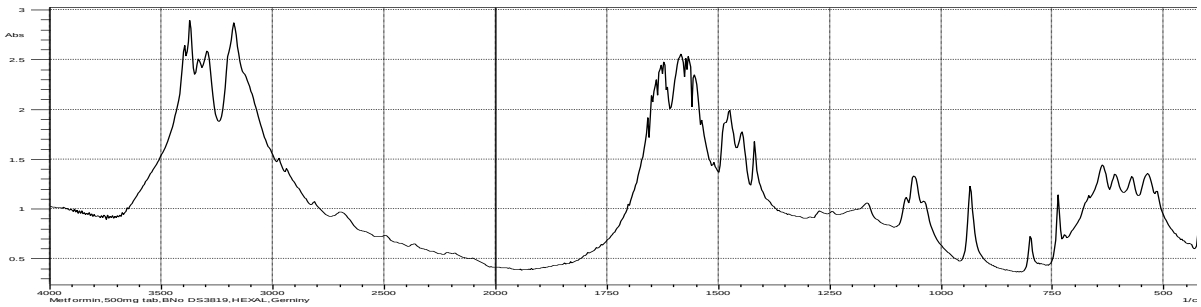

Figure 3: FTIR spectra of Brand B Metformin.

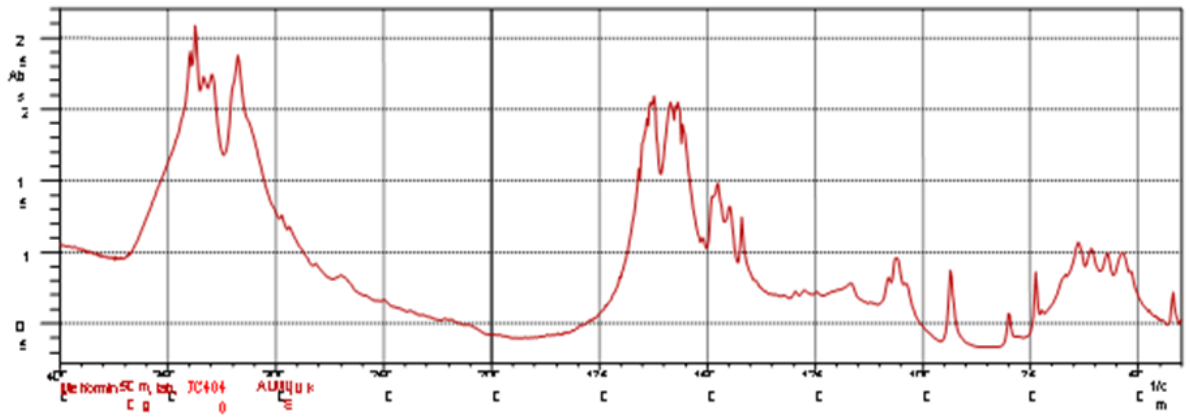

Figure 4: FTIR spectra of Brand C Metformin.

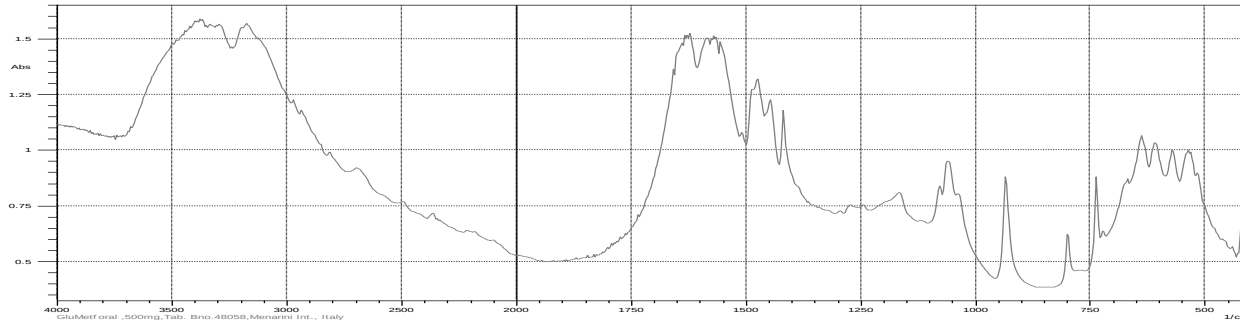

Figure 5: FTIR spectra of Brand D Metformin.

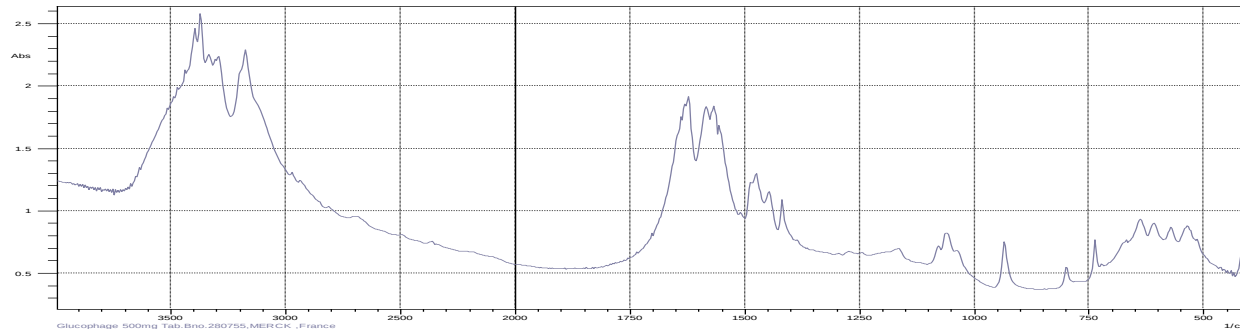

Figure 6: FTIR spectra of Brand E Metformin.

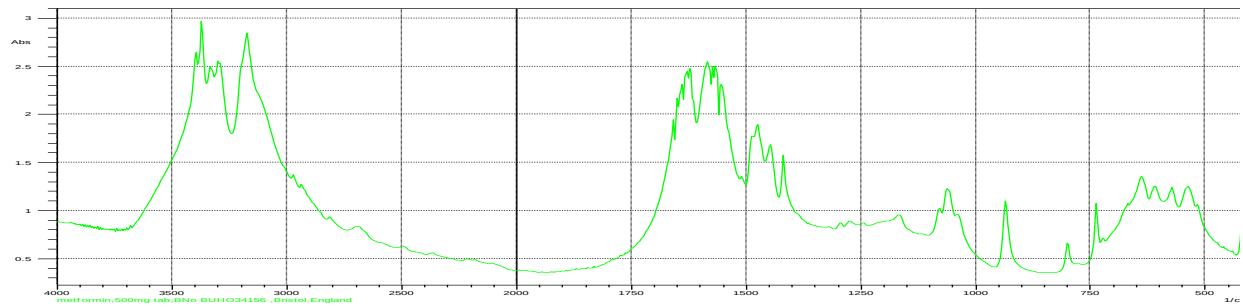

Figure 7: FTIR spectra of Brand F Metformin.

CONCLUSIONS

Six brands of Metformin 500 mg tablets have been subjected to analysis according to the Pharmacopoeia. The results have shown that all the tested brands satisfied the requirement of all testes applied except in term of hardness where 3 brands were harder than the other which effect on disintegration and dissolution but within the acceptable limit. The study proved the physicochemical equivalency of the six brands so could be considered bioequivalence and therefore can be substituted with each other in clinical practice. According to the present study emphasizing the need of constant inspection on marketed drug product by the government, manufacturers and independent research

groups to ensure supply and availability of quality medicines for the patients and *in vitro- in vivo* bioequivalence.

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