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COMPARATIVE EVALUATION OF DIFFERENT BRANDS OF ENTERIC-COATED DICLOFENAC SODIUM TABLETS

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ABSTRACT: Diclofenac sodium is a non-steroidal anti-inflammatory drug with wide use in the treatment of rheumatic diseases. Enteric-coated tablet form of this drug has been developed to prevent the gastric irritation problem encountered with its use and to improve its efficacy. The enteric film coat resists solution in gastric fluid and disintegrates and releases the medication in the intestines. Many brands of enteric coated tablets of diclofenac sodium are manufactured and sold in the market. However, there is a real concern that counterfeited drugs and drugs with poor pharmaceutical quality could enter the Libyan market. In this study, the physicochemical quality of four brands of diclofenac sodium 50 mg enteric-coated tablets was assessed and compared in terms of visual inspected characters, diameter, thickness, weight uniformity, hardness, friability, disintegration time, dissolution, and drug content. The brands compared were Voltarène™ (brand A), Diclofenac Normon™(Brand B), Neoflam™ (brand C), and Divon™ (brand D). As expected, brand A showed acceptable results considering it to be the original brand name drug. Brands B and D also exhibited comparable results to that obtained with brand A. Therefore, it is expected for these brands to behave similarly *in vivo* and can be efficiently interchanged. Brand C exhibited lower solidity, inability to avoid disintegration in acidic medium, and an earlier release profile. Consequently, tablets are unable to maintain their integrity in the stomach leading to gastric irritation and poor bioavailability.

INTRODUCTION: The oral route of delivery is the most preferred administration route as it offers one of the safest and most convenient methods of drug administration. Tablets are single-dose solid dosage units manufactured by single or multiple compression. Some types of tablets are produced by molding or extrusion techniques [1]. Tablets contain one or more active ingredient usually with additives such as diluents, disintegrants, binders, lubricants, glidants, flavors, and coloring agents [2].

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Tablet excipients must be compatible with each other and with the drug and must improve tablet stability and pharmaceutical quality. Tablet coating is one of the solutions to overcome the limitations that are associated with compressed tablets. Enteric-coated tablets are compressed tablets coated with an inert substance which resists dissolution in gastric juices, but freely dissolves and liberates the drug in the intestines [2, 3].

Enteric-coating provides protection for acid-labile drugs against decomposition, prevents gastric distress due to irritation, delivers drugs to the intended local site of action in the intestine, delivers drugs to their optimum site of absorption in the intestine, provides a delay-release component for repeat action tablets, stabilizes the principal ingredients, enhances the appearance, and masks

unpleasant taste and odor of tablets [4, 5]. Enteric coating is achieved by substances such as cellulose acetate phthalate and copolymers of methacrylic acid and its esters. The type of the polymer and the thickness of the enteric coat film layers control the solubility of the coat [4, 6].

Gastrointestinal transit and pH profiles are major factors in predicting and controlling the drug release performance of enteric-coated tablets [7-11]. Diclofenac sodium, [*o*-(2,6-dichloro-phenyl) – amino - phenyl] acetate ($C_{14}H_{10}Cl_2NNaO_2$, M.W. 318.14), is a potent non-steroidal anti-inflammatory drug with pronounced anti-rheumatic, anti-inflammatory, analgesic, and antipyretic activities [12]. It is poorly soluble in acidic medium and highly soluble in basic medium, therefore, the pH affects its solubility, absorption, hence its efficacy [13, 14]. The enteric-coated tablet form of diclofenac sodium allows the drug to by-pass the stomach to the intestine for better dissolution, absorption, and to avoid its irritating effect on gastric mucosa for better patient compliance [15]. Generic drug products have lower development costs, thereby, have cheaper selling prices in comparison to the original innovator formulations. Although generic drugs contain the same active principal ingredients, differences have been demonstrated in their quality and efficacy due to differences in formulation techniques and excipients used [16-19]. The Libyan market is enriched with various generic brands of diclofenac sodium 50 mg enteric-coated tablets beside the brand name one. However, there is no guarantee that all the marketed drugs in Libya have been subjected to strict approval processes by relevant regulatory agencies, indicating that counterfeited medications and that with substandard quality can easily find their way into the market. The aim of this work was to evaluate and compare the pharmaceutical quality of different brands of diclofenac sodium 50 mg enteric-coated tablets dispensed in Libya.

MATERIALS AND METHODS:

Materials:

Samples of four commercial brands of enteric-coated diclofenac sodium 50mg tablets were purchased from several private pharmacies in Tripoli (**Table 1**). All samples were assessed within their valid shelf-life. Diclofenac sodium pure RS was obtained from the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tripoli-Libya. The reagents, hydrochloric acid (Fisher Chemicals, New Jersey, USA), sodium orthophosphate $Na_3PO_4.12H_2O$ (Avonchem Ltd., Macclesfield, UK), sodium hydroxide were of analytical grade and used in the study.

TABLE 1: DICLOFENAC SODIUM 50 mg ENTERIC-COATED TABLETS EVALUATED IN THE STUDY

Brand	Brand name	Manufacture Date	Expiry Date	Batch No.	Manufacturer
A	Voltarène	06/2013	06/2017	13002	Novartis, Tunisia
B	Diclofenac Normon	03/2013	03/2016	H18A1	Laboratorios Normon, S.A., Spain
C	Neoflam	03/2012	03/2015	DSB2002	Neopharma, UAE
D	Divon	12/2011	11/2014	DQTP0068	Micro Labs Ltd., India

Methods:

Tablet Appearance:

Samples of 20 tablets from each batch were randomly selected and their apparent properties such as color, shape, surface shape, presence of grooves & monograms, and coat were described based on the visual observation.

Weight Uniformity:

The individual weight of twenty tablets selected randomly from each brand was measured and recorded. The average weight of each sample was calculated and the deviation of each tablet weight from the average weight was determined. The batch is considered to comply with the USP specifications if the weight of not more than 2 of the tablets differs from the average weight by no more than the percentage permitted and no tablet differs by more than double that percentage.

Hardness and Tablet Dimensions:

The hardness, thickness, and diameter of a sample of 10 tablets were determined using tablet combination tester (PTB311E multicheck tester,

Pharma test, Germany). In the hardness test, pressure was applied on the tablet along its diameter and the force causing the tablet to break up was recorded. The optimum hardness regarded for coated tablets is 10-20 kg/cm^2. Tablet thickness and diameter should be controlled within a ±5% of a standard value.

Friability:
Samples of 10 tablets from each batch were selected randomly and weighed. Tablets were placed in the plastic chamber of the friabilator (PTF 20E Pharma test, Germany) and allowed to rotate and drop a distance of 6 inches at each revolution for 100 revolutions (25 rpm/minute). The tablets were removed, de-dusted, reweighed, and the percentage friability was calculated using the following equation:

$$\%F = \frac{WI - WF}{WI}$$

Where WI=Initial weight of tablets, WF=tablets weight after friability test.

Disintegration Time:
Samples of six tablets were selected from each of the different brands. Tablets were placed in the six tubes of the basket-rack assembly of the disintegration time tester PTZ Auto 1EZ (Pharma test, Germany) and perforated cylindrical plastic discs were put on the top surface of each tablet. The assembly was allowed to move up and down in a beaker containing 1 liter of 0.1N HCl at 37±2°C simulated fluid at 28-32 cycles/minute for 2 hours. Then HCl was replaced with 1 liter of prewarmed phosphate buffer pH 6.8 and the disintegration was resumed for 1 hour. The BP limit states that tablets should remain intact for 120 minutes in acidic medium and then disintegrate during one hour in an alkaline medium.

Standard Calibration Curve for Diclofenac Sodium:
Standard stock solution of diclofenac sodium (0.1mg/ml) was prepared by dissolving 10 mg of drug in phosphate buffer (pH 6.8). Serial dilutions (5-30 µg/ml) were made from the stock solution and absorbance was determined at 276 nm in a UV-Visible spectrophotometer Jenway 6305 (Bibby Scientific Ltd., UK).The curve was plotted and linear equation was y=0.0297x, R^2=0.9928.

Dissolution Rate:
The dissolution test was conducted using the paddle method (USP Apparatus II) in the dissolution tester PTDT70 (Pharma Test, Germany). The vessels were filled with 900 ml of 0.1N HCl and heated to 37±0.5°C. One tablet was placed in each vessel and the paddles were operated at 100 rpm. Samples of 5 ml were withdrawn from each vessel after 30 and 60 minutes and absorbance was determined at 276 nm using a UV-Visible spectrophotometer Jenway 6305 (Bibby Scientific Ltd., UK).Vessels were then emptied from HCl and filled with prewarmed phosphate buffer (pH 6.8). Samples of 5 ml were collected at time intervals of 5, 10, 20, 40, and 60 min. Samples were filtered, diluted when required, and the absorbance was measured at 276 nm.

Drug Content:
The drug content in tablets was determined by randomly choosing ten tablets from each brand. The tablets were powdered using a mortar and pestle and a quantity equivalent to 50 mg of diclofenac sodium was weighed and dissolved in methanol. After suitable dilutions, solutions were analyzed by using a UV-Vis spectrophotometer at ʎ max 276 nm.

RESULTS AND DISCUSSION:
The study was based on comparative assessment of the pharmaceutical quality of original formulation (Brand A) and generic drugs (Brands B, C, & D) of diclofenac sodium 50 mg enteric-coated tablets (**Table 1**). The products were investigated for their compliance with the standard pharmaceutical requirements that are stated in the official compendia. The apparent physical characteristics of the samples based on visual inspection are described (**Table 2**). All the tablets were round in shape with attractive and uniform colors ranging from pale yellow to brownish yellow. All the brands were biconvex-faced tablets, except brand A tablets were flat-faced with beveled edges. As indicated (**Table 2**), there were no defects in the color homogeneity or coat integrity and gloss of the tablets and tablets did not bear break marks. All

the studied brands were consistent in their diameters and thickness (**Fig.1**).

TABLE 2: APPEARANCE FEATURES OF THE DICLOFENAC TABLET BRANDS

Parameter	Brand A	Brand B	Brand C	Brand D
Shape & color	Round & brown-yellow	Round & pale yellow	Round & brown-yellow	Round & orange
Surface texture & Convexity	Smooth & Flat-beveled edges	Smooth & Biconvex	Smooth & Biconvex	Smooth & Biconvex
Monograms & score line	GT on one side, CG on the other	None	U on one side	None
Defects in the tablet coat	None	None	None	None

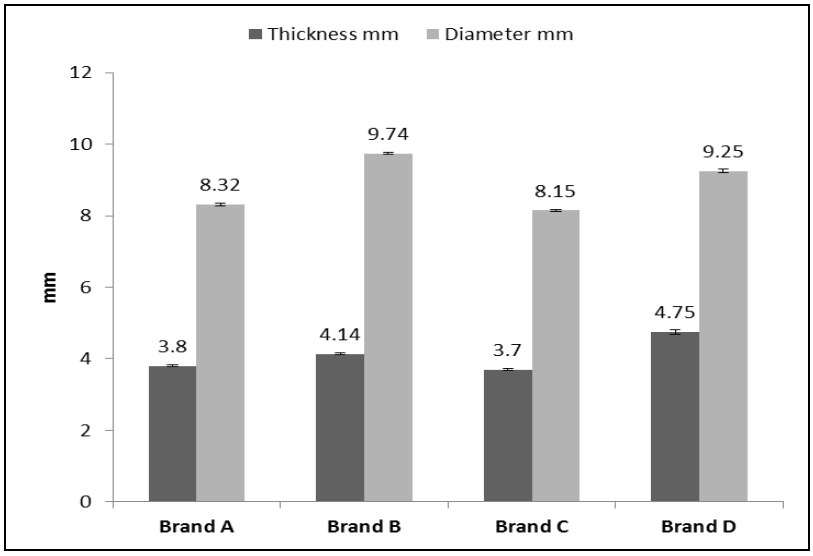

FIG.1: THICKNESS AND DIAMETER OF DICLOFENAC SODIUM TABLET BRANDS (MEAN VALUE ± SD, n=10)

Uniformity of tablet diameter, thickness, and mass of a produced batch or batches of the same formulation is an essential requirement. Results of weight variation test revealed that all samples complied with acceptance limits (**Table 3**). The deviation of tablet weights from the average weight was within the official specification (±7.5%). Brands A and C exhibited quite similar average weight and brands B and D were similar. Differences in the mean weights indicate implementation of different types of excipients in each formulation. Unacceptable deviation in tablets total mass provides a clear indication of inconsistency in drug for tablets designed with low level of active ingredient(s). In the manufacturing of tablets, proper formulation design and precise adjustment and control of all factors and parameters that govern the physicochemical properties of the tablets will reflect positively on their pharmaceutical quality.

TABLE 3: AVERAGE WEIGHT, WEIGHT VARIATION, FRIABILITY, HARDNESS AND DRUG CONTENT OF DICLOFENAC SODIUM BRANDS (MEAN VALUES ± SD, n=3)

Brand	Average weight g	Weight variation %	Friability %	Hardness kg/cm^2	Drug content %
A	0.216±0.004	-0.076±2.107	0.15±0.002	16.22±1.51	98.16
B	0.277±0.011	-0.249±2.374	0.0±0	16.32±1.15	97.26
C	0.203±0.005	-0.650±2.835	0.16±0.002	09.13±0.74	102.23
D	0.278±0.006	-0.417±2.367	0.0±0	11.03±1.49	105.72

The hardness test results (**Table 3**), showed that brands A, B, and D exhibited greater capability to resist chipping than C. Brand C demonstrated the lowest and weakest solidity in comparison to the other brands. All the brands of diclofenac sodium enteric-coated tablets were with acceptable friability (< 0.5 to 1.0%). In general, tablets should be with sufficient hardness to withstand stress of

handling, packaging, and shipping and with enough softness to disintegrate easily and properly after administration. The results of the disintegration time test showed that brands A, B, and D passed the test according to the official limits (**Table 4)**. While brand C exhibited slight cracking characters in the acidic medium and showed very fast disintegration in the alkaline medium. It was observed from the disintegration test data that brands A, B, and D demonstrated optimum stability in the acidic medium, as the tablets remained intact and did not show any cracking or softening. Brand C demonstrated low hardness in comparison to the other brands and showed disintegration time that was outside the limits for enteric coated tablets.

It has been proved that coating characteristics control the acidic resistance capability of the tablets [20]. The compression force used in tablet production also plays an important role in the control of tablet solidity, where the greater the compression force used, the harder the tablet will be produced [21]. In addition, the granulation characteristics also determine the solidity of the tablets.

TABLE 4: DISINTEGRATION TIME OF DICLOFENAC SODIUM BRANDS (MEAN VALUE ± SD, n=3)

Brand	HCl hr:min:sec.	Phosphate buffer pH 6.8 hr:min:sec.
A	No disintegration after 120 min.	00:12:19±0.001
B	No disintegration after 120 min.	00:13:31±0.001
C	Cracking occurred after 01:38:19±0.008	00:03:58±0.002
D	No disintegration after 120 min.	00:14:33±0.005

It was found that all brands were in compliance with the standard limit for dissolution test, where after 45 minutes not less than 70% of the drug was liberated in the buffer (**Fig.2**). The brands showed poor release profiles in the acidic environment, where less than 10% and optimum release in pH 6.8 simulated intestinal medium. This is in agreement with other studies where the drug was released very poorly in the acidic medium and efficiently in simulated intestinal fluid [22-26]. The drug release performance of brands B and D were comparable to that observed with brand A [27, 28]. High similarity and equivalence in drug dissolution pattern to the innovator was seen with Brand D, where similarity factor F2 was 57.72 and difference factor F1 was11.31.

The time required for 50% of drug to be released ($t_{50\%}$) from brands A, B, C, and D were 80, 86.3, 69.5, and 82.2 minutes, respectively. The $t_{50\%}$ was decreased in the order of B then D then A then C. Brand C exhibited the earliest and fastest drug release figure compared to the other brands, where drug was completely released after only 20 minutes. Brand C tablets also could not resist disintegration in the acidic medium, which may be due to their lower ability to resist crushing. In addition, employment of different production processes and different excipients can affect drug release from tablets [29, 30]. Drug content of diclofenac sodium from all formulations was found in the range 97-105%, which was within the USP specified limit (90-110%).

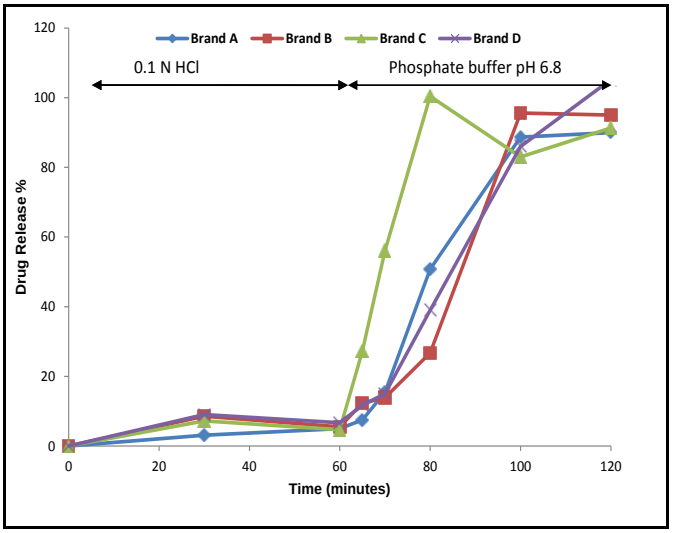

FIG. 2: *IN VITRO* DRUG RELEASE PROFILES OF THE DICLOFENAC SODIUM TABLET BRANDS

CONCLUSION: All brands demonstrated elegant and attractive external features. Tablets were consistent in diameter, thickness, and weight. Brands A, B, and D exhibited sufficient mechanical strength to resist fracture and attrition. Additionally, these brands showed acceptable disintegration time, drug release pattern and drug content. Therefore, switching between these products could be managed with successful efficacy. However, brand C showed low solidity

compared to the other brands, its disintegration time was not in compliance with the official limits and showed an accelerated dissolution profile.

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