

PHYSICOCHEMICAL EQUIVALENCE OF DIFFERENT BRANDS OF DICLOFENIC SODIUM SR TABLETS AVAILABLE IN LOCAL MARKET

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Article Received on: 06/09/11 Revised on: 10/10/11 Approved for publication: 04/11/11

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ABSTRACT

The aim of the present study is to determine the Pakistani market condition for the healthcare of patients suffering from different pain condition e.g. arthritis, and also to correlate the quality with the cost of the brands. The present study is concerned to scrutinize and compare the physicochemical equivalence of different brands of sustained release tablets containing Diclofenac sodium purchased from different retail pharmacy outlets. The physicochemical equivalence of five different brands of Diclofenac sodium SR tablets was evaluated. These brands were tested through different statistical methods in accordance to the guidelines given in BP i.e. Weight variation, diameter, thickness, hardness, friability, dissolution, assay, price, expiry and appearance. Only two brands passed the dissolution test, one brand tablets were completely dissolved within first two hrs and remaining brands fail the dissolution test. Similarly problem was found in thickness of the different brands tablet. However no major problem was found in tablet weight variation, assay, diameter, friability, hardness parameter.

KEYWORDS: Diclofenac Sodium SR tablet, National and Multinational firm, Comparative evaluation, physicochemical properties.

INTRODUCTION

The increase in the number of generic drug products has placed health care people to select one from among several seemingly equivalent products². For instance, in 1975 approximately 9% of all prescription drugs dispensed in the United States were generic versions². This figure rose to 20% in 1984 and 40% in 1991¹. Over 80% of the approximately 10,000 prescription drugs available in 1990 were obtained from more than one source and variable clinical responses to these dosage forms supplied by two or more drug manufacturers is documented. These variable responses may be due to formulation, packaging and storage and even the rigors of in-process quality control. Pakistan as a developing country offers a growing market for pharmaceuticals. All categories of the products are the research product of multinational firm which are reformulated and marked by these national firms. Moreover the multinational firms claim that their high price are due to the overheads like research, high salaries of employee, maintaining GMP, GLP plus importing raw material from mother plants. The national firm claims that their products are not at all inferior to the products of multinational firm. It was in view of this fact that the W.H.O issued guidelines for global standard and requirements for the registration, assessment, marketing, authorization and quality control of generic pharmaceutical products⁴. Preliminary physicochemical assessment of the products is very important and in vitro dissolution testing can be a valuable predictor of the in vivo bioavailability and bioequivalence of oral solid dosage forms^{2,3}.

To produce significant sustaining effects and to increase the bioavailability of drug, the Modified Release (MR) dosage forms have made significant progress in terms of clinical efficacy and patient compliance. The degree of precision of control over the rate of drug release from MR dosage form varies according to the particular formulating techniques employed⁵. It is necessary to have comparative bioavailability of conventional (IR) as well as SR formulations^{6,7}.

Diclofenac sodium (DS) is administered orally in the treatment of rheumatoid arthritis, osteoarthritis and also for a variety of nonrheumatic inflammatory conditions⁸. It has short biological half-life and hazards of adverse gastrointestinal (GI) reactions⁹. The development of oral sustained-release formulations of this drug is highly desirable¹⁰, in order to achieve improved therapeutic efficacy

and patient compliance. In this study different brands of Diclofenac Sodium SR tablets were tested for their physical parameters and in-vitro release study

MATERIALS AND METHOD

Five brands of Diclofenac Sodium SR tablets were purchased from the local market and were tested through various physical and chemical methods such as, Weight variation, Diameter, Thickness, Hardness, Friability, Dissolution and Assay.

Weight Variation:

20 tablets were selected randomly and weighed individually. The average weight was calculated and individual weight was compared to the average weight. The tablet passes the test according to British Pharmacopoeia if not more than two of the individual weights deviate from the average weight by more than $\pm 7.5\%$ and for one product limit was $\pm 5.0\%$ ¹¹.

Diameter

In BP the stated diameter can deviate by $\pm 5\%$ up to 12.5 mm and by $\pm 3\%$ above 15mm. Using Diameter Tester, Pharma Tester, and the diameter of 10 tablets were determined¹¹.

Thickness

Thickness of tablet can fluctuate without any change in its weight because of variation in the granules density, pressure and Speed of tableting machine. Tablet thickness was determined by Pharma Tester that measures the thickness in millimeters. Allowed Limit is $\pm 5\%$, depending on the size of the tablet¹¹.

Hardness

Tablet hardness depends on pressure applied, dwell time and nature of formulation. Hardness of 10 tablets was measured by the Pharma Tester¹¹.

Friability

The friability test shows the abrasion tendency of tablet during manufacturing and supply process. For this purpose 20 tablets were selected randomly and weighed individually, then placed in the friabilator. It was then operated for 100 revolutions. The tablets were then dusted, reweighed and percent loss was calculated. Allowed Limit is not more than 1% of the weight of the tablets being tested¹¹.

Assay

Tablet contain specific amount of active ingredients with allowable variable limit. Assay of tablet ensure active drug and stability of product. 20 tablets were weighed, powdered and equivalent to 50

mg of Diclofenac sodium powdered was weighed and dissolved in 100 ml volumetric flask using 0.1 N NaOH. The solution was filtered and 2 ml of this sample solution was taken and dissolved

in 100 ml volumetric flask by 0.1N NaOH. Absorbance was measured at 276 nm using 0.1 N NaOH as a blank by spectrophotometer and percent purity was determined¹³.

$$\text{Diclofenac Sodium \%} = \frac{\text{Abs. of sample} \times \text{Wt. of Std.} \times \text{Av. Wt. of tablet} \times 100}{\text{Abs. of Std.} \times \text{Wt. of sample}}$$

Dissolution

Dissolution test evaluate factors that affect the bioavailability of a drug from a solid dosage form. During dissolution test drug passes into solution is studied as a function of time and thus describes the over all rate of drug release. The dissolution test was conducted using simulated gastric fluid (0.1N HCl) and intestinal fluid (phosphate buffer pH 6.8) as dissolution medium. Using simulated gastric fluid, 900 ml of 0.1N HCl was placed in the vessel and allowed to come to 37 ± 0.5°C. Then, Diclofenac sodium tablets were placed in all the six vessels, one in each vessels and stirrer was rotated at 100 rpm for 2 hrs. At the end of 2 hrs, tablets were removed from each vessel and immediately placed in 900 ml of phosphate buffer (pH 6.8) at same rotation speed and temperature as mentioned above for 8 hrs. After predetermined intervals of 2, 4, 6 and 8 hrs, sample of 10 ml was pipetted out and same volume of fresh phosphate buffer was added to keep volume of the dissolution medium constant. The sample was diluted to 100 ml and the absorbance was measured at 276 nm and dissolution was calculated using Beer's Lambert law. Similarly, the absorbance of known

concentration of standard solution of Diclofenac sodium was measured and percent drug release was calculated^{12,13}.

Data analysis: Data for weight uniformity test, diameter, thickness, friability and hardness of the tablets were analyzed by determining the mean ± standard deviation.

RESULTS AND DISCUSSION

In current project physicochemical properties of the five brands of Diclofenac sodium (50mg) SR tablet were evaluated in order to identify the relative difference in quality parameters and its effect on the release of drug from the dosage form.

Weight Variation

The significance of this test is to ensure that the tablets in each lot are within appropriate range size and contents are calculated on average tablet weight basis. From table 1 and figure 1, it is clear that all tablets are in the range except two tablets cross the upper limit (321,321mg) of product code AOV 001 and for product code DYD 004 only one tablet crosses upper limits (199 mg). The possible reason for the difference in weight variation may be due to the machine problem or the coating process¹³.

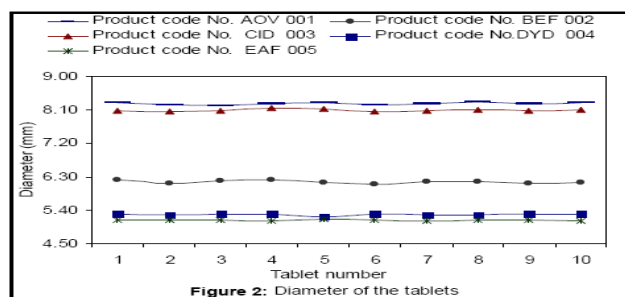
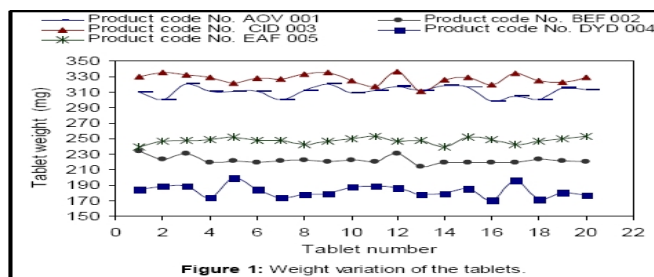
Table 1: Product code with Appearance, Expiry date, Relative price, Average weight, diameter, thickness, hardness (mean ± s. d.), friability and assay % of the tablets

Product Code No.	Appearance	Expiry (years)	Relative Price (%)	Avg. weight (mg)	Avg. diameter (mm)	Avg. thickness (mm)	Avg. hardness (N)	Friability %	Assay %
AOV001	Biconvex Film coated tablet	5	100	305.000 ± 6.656	8.27 ± 0.03	0.864 ± 0.068	14.87 ± 0.87	0.06	97.310
BEF 002	Triangular Biconvex film coated tablet	3	51	222.550 ± 4.651	6.16 ± 0.04	0.390 ± 0.079	80.52 ± 9.50	0.22	102.531
CID 003	Biconvex film coated tablet	3	83	327.25 ± 6.528	8.09 ± 0.03	1.419 ± 0.100	203.90 ± 22.24	0.24	98.575
DYD004	Triangular biconvex film coated tablet.	4	38	182.85 ± 7.721	5.29 ± 0.02	0.450 ± 0.073	71.32 ± 21.74	0.16	96.361
EAF 005	Biconvex square film coated tablet.	3	96	247.700 ± 7.721	5.13 ± 0.01	1.736 ± 0.037	173.66 ± 12.35	0.20	94.620

Diameter and Thickness

These are important for Blister/strip packaging. From table 1 and figure 2 it is clear that the diameter was in the range of 5.13 ± 0.01 to 8.27 ± 0.03 mm. So the diameters of all the tablets are in the range (± 5%)

From table 1 thickness was in the range of 0.390 ± 0.079 to 1.736 ± 0.037 mm. From table 1 and figure 3 it is clear that the thickness of product code AOV 001, three tablets cross lower limit (0.78, 0.79, 0.81 mm) and one tablet cross upper limits (1.00 mm). For product code BEF 002, five tablets cross lower limit (0.27, 0.32, 0.33, 0.33, 0.37 mm) and three tablets cross upper limits (0.42, 0.45, 0.51 mm). For product code CID 003, four tablets cross lower limit (1.30, 1.32, 1.33, 1.34 mm) and two tablet cross upper limits (1.55, 1.58 mm). For product DYD 004, four tablets cross lower limit (0.35, 0.35, 0.39, 0.41 mm) and five tablets cross upper limits (0.48, 0.49, 0.51, 0.52, 0.56 mm). For product EAF 005, the entire tablets are within the range. The possible reason for the difference in thickness may be due to weight variation, hardness variation or variation in the granules density, pressure and speed of tableting machine or the coating process.



Hardness and Friability of the tablets

From table 1 and figure 4 it is clear that the hardness all tablets is in the range of 14.87 ± 0.87 to 203.90 ± 22.24 , but variation exist among the tablets.

From table 1 and figure 5 it is clear that, friability of the five different brands is less than 0.25 %. Therefore, it complies the BP standards^{12,14}.

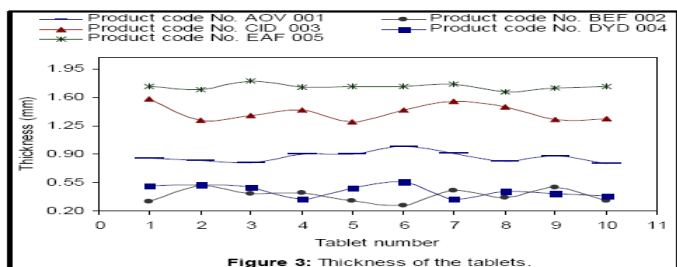


Figure 3: Thickness of the tablets.

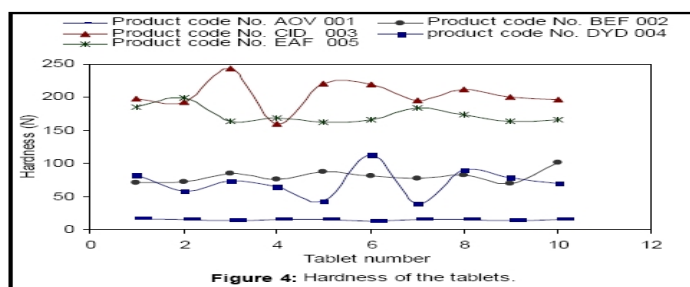


Figure 4: Hardness of the tablets.

Table 2: Dissolution % of the tablets at different times

Two hrs	Limit %	Code No. AOV001	Code No. BEF002	Code No. CID003	Code No. DYD004	Code No. EAF005
1 st	15 - 30	17.84	24.67	15.75	6.976	97.41
2 nd	25 - 50	30.686	39.006	22.47	10.486	-----
3 rd	35 - 70	44.314	49.77	28.57	14.83	-----
4 th	NLT 70	90.386	72.84	32.160	21.145	-----

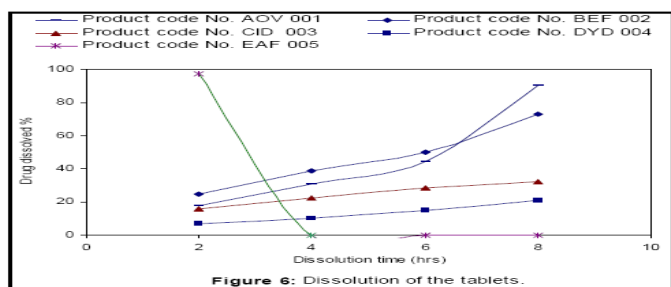


Figure 6: Dissolution of the tablets.

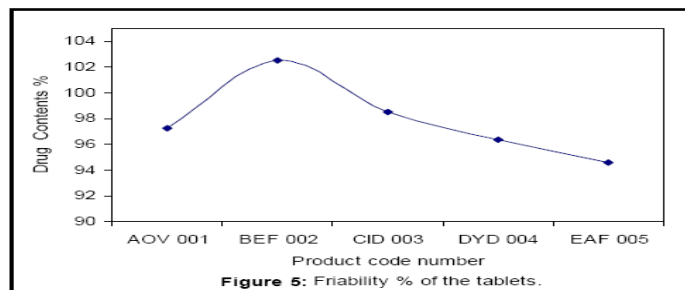


Figure 5: Friability % of the tablets.

Dissolution test

Dissolution test is the measure of the amount of drug released in the dissolution medium within time. Dissolution test was carried out in six tablets of each brand. The % age drug released was analyzed in both 0.1 N HCl and in phosphate buffer (pH 6.8). From table 2 and figure 6 it is clear that for product code AOV 001 and BEF 002, the results are with in range. While for product code CID 003, the 1st limit is within the range but 2nd and 3rd limit are below from lower limits and 4th limit is very below from lower limit. For product DYD 004, all the four limits are very below from lower limits. For product EAF 005, the entire six tablets were completely dissolved in the 1st two hrs. The possible reason for this difference in dissolution rate may be due to difference in surface area of the drug particles¹⁵ or the nature of excipients used or the formulation process. It has been shown by Abdou¹⁶ that dissolution rate of a drug can be altered significantly with various adjuncts manufacturing process.

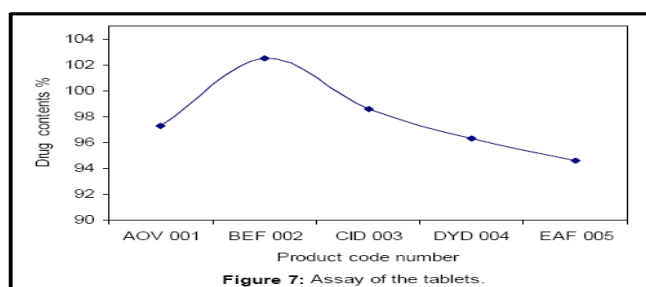


Figure 7: Assay of the tablets.

Pharmaceutical Assay

Using UV spectrophotometer, pharmaceutical assay was carried out for all the five brands of Diclofenac sodium. The limit of pharmaceutical assay according to the specification of BP is 90-110%. From table 1 and figure 7 it is clear that the pharmaceutical assay of the five different brands is within the range. Lowest content is 94.620 % while highest content 102.531 %.

Expiry, Price and Appearance

It has been noted during the present study that there is a lot of difference in the price, expiry date and appearance of national and multinational pharmaceutical products. From table 1 it is clear that, the product code AOV 001 has the highest expiry date of 5 years while product code DYD 004 has the second highest expiry date of 4 years and the remaining three products has the lowest expiry date of 3 years. On the other hand, the product code AOV 001 has the highest price with good quality, but product code BEF 002 has good quality with very low price, while the product code CID 003 and EAF 005 has high price with low quality. The tablets of two products AOV 001, CID 003 are biconvex; while the tablets of two products BEF 002, DYD 004 are triangular biconvex and the tablets of EAF 005 are biconvex square.

CONCLUSION

Close monitoring of different process in Pharmaceutical industries will reduce the production time and cost, as well as will improve the quality of the product. It was found that dissolution was the critical parameter where problem exist among different brands. Only two brands passed the dissolution test, tablets of one brand were completely dissolved within 1st two hrs while remaining brands fail the dissolution test. Similarly problem was found in thickness of the different brands. However no major problem was found in tablet weight variation, assay, diameter, friability and hardness. Also, it was noted that some of the local firm has very low price as compared to the multinational firm having the same good quality but some local firm has nearly the same price as that of multinational with low quality. It was concluded that the different brands of well reputed local pharmaceutical firms can be compared with that of multinational firms, however products of some less known local firms needs improvement in quality but some local firm should be strictly monitored for manufacturing of control release dosage form. This study also infancies the need for constant market monitoring of new products to ascertain their equivalency to the innovator products.

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Source of support: Nil, Conflict of interest: None Declared